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Synthesis of 9-Deoxotaxane Analogs

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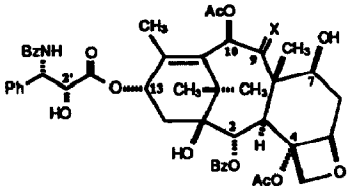
Abstract: *The synthesis of 9-deoxotaxol (9) ,7,9-dideoxy and 7,9,10-trideoxygenated analogs is described starting from 13-acetyl-9(R)-dihydrobaccatin III.*

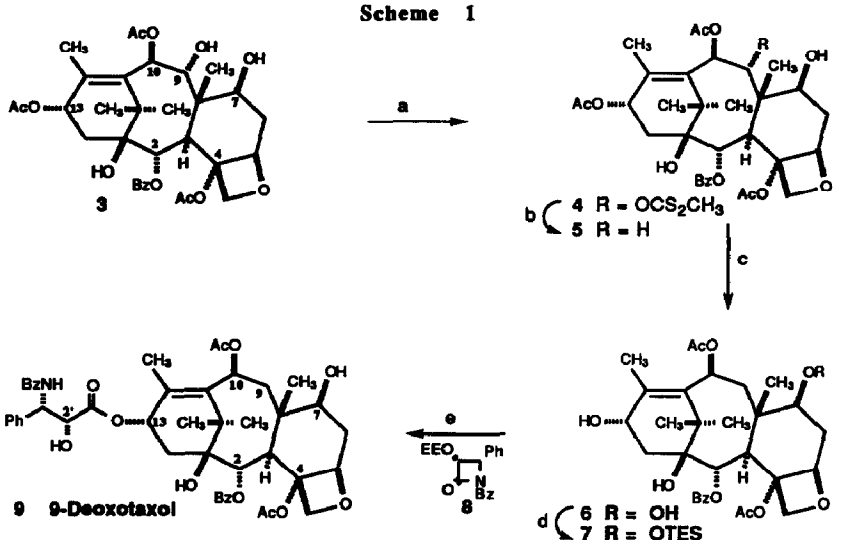
The naturally occurring diterpene taxol (**1**) has exhibited effective antitumor activity against ovarian and breast tumors in clinical trials.[1] We have recently reported the synthesis of 9(*R*)-dihydrotaxol[2] (**2**) and other analogs[3] obtained from a new congener isolated from *Taxus canadensis*, 13-acetyl-9(*R*)-dihydrobaccatin III (**3**).[4] The fact that **2** shows similar antitumor activity to taxol prompted us to study the requirement for functionality at C-7, C-9 and C-10. In light of recent reports by others,[5] we report here our results regarding removal of the C-9 functionality from the taxane skeleton toward the synthesis of 9-deoxotaxol and its analogs.



1 X = O Taxol
2 X = H, α-OH 9(R)-Dihydrotaxol

Treatment of **3** with thioacylating agents such as thiophosgene, thiocarbonyldiimidazole(TCDI), or phenyl chlorothionoformate led to formation of the cyclic 7,9-thionocarbonate which did not serve as a good substrate for deoxygenation. The ready formation of this cyclic product reflected the positioning of the C-7 and C-9 hydroxyl groups which have been shown to exist in a 1,3-pseudoequatorial array in the crystal structure of **3**. Alternatively, when **3** was treated with lithium hexamethyldisilazide in tetrahydrofuran at -78°C followed by carbon disulfide and methyl iodide, we cleanly obtained a mono-xanthate derivative **4**; however, since acylation or silylation of **3** usually takes place at the less hindered C-7 center, it was surprising to find that this product was the C-9 rather than the C-7 methyl xanthate. This C-9 xanthate **4** was subsequently treated with tributyltin hydride under standard conditions

Scheme 1



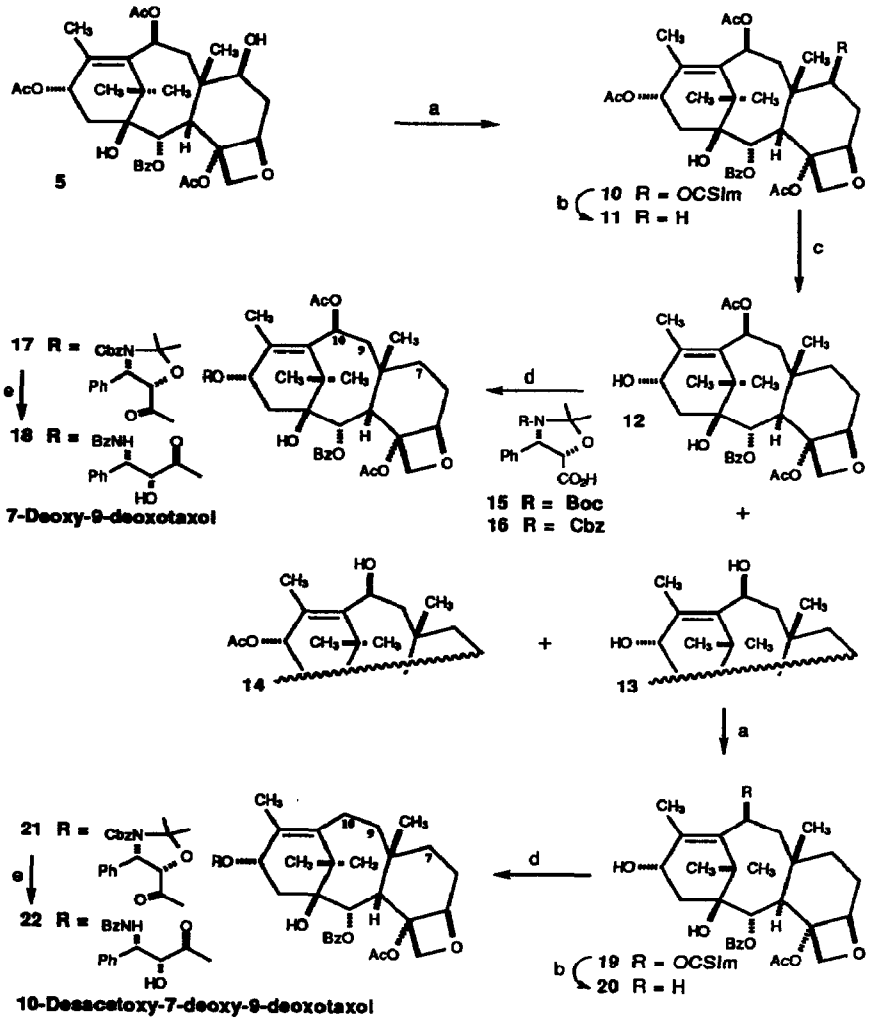
(a) LiHMDS, CS_2, CH_3I, THF 72%; (b) Bu_3SnH, AIBN, PhMe 95%; (c)CH_3Li, THF 50%; (d) TESCl, TEA, DMAP 90%; (e) i. Lactam **8**, LiHMDS, THF; ii. 1% HCl, EtOH, 30% for 2 steps.

and smoothly led to 9-deoxo-13-acetylbaccatin III (**5**). This is the first report of a deoxygenation at the C-9 position.

Our previous report on the preparation of 9(R)-dihydrotaxol[3] described the use of nucleophilic reagents such as n-butyllithium for the first selective deacylation of a taxane C-13 acetate. Similar treatment of **5** with methyllithium afforded 9-deoxobaccatin III (**6**) in 50% yield. Protection of the more reactive C-7 hydroxyl group with triethylsilyl chloride (TESCl) gave **7** in 90% yield. Acylation of **7** with the lactam **8**[6] and mild deprotection of the 2'-O-ethoxyethyl and TES groups afforded 9-deoxotaxol (**9**) in 30% yield.[7]

Compound **5** could also be treated with thiocarbonyldiimidazole to give the 9-deoxo-7-thiocarbonylimidazolide **10**. This compound underwent straightforward deoxygenation as before using the tin hydride reagent to give 9-deoxo-7-deoxy-13-acetylbaccatin III (**11**). Unlike many other cases of C-13 deacetylation which have been attempted in our laboratories, the deacetylation of **11** with methyl lithium took place in a relatively nonselective manner affording three products: the desired 13-deacetyl analog **12**, the 10,13-dideacetyl compound **13**, and a minor amount of the 10-deacetyl compound **14**. These products were separated by chromatography and compound **12** was treated with lactam **8** as above to give only a low yield of adduct. The fact that both the deacetylation and the reacylation of C-13 were atypical suggests that under these strong base conditions, different conformations may exist for the deoxygenated compounds which affect the chemistry of the remaining functional groups.

Scheme 2



(a) TCDI, DMAP, PhMe 88% for **10**; 90% for **19**; (b) Bu_3SnH, AIBN, PhMe 94% for **11**; 71% for **20**; (c) CH_3Li, THF 58% (12:13 (3.1:2.7); (d) Acid **16**, DCC, DMAP 82% for **17**; 76% for **21**; (e) H_2, 10%Pd/C, aq. CH_3OH / Bz_2O, 74% for **18**; 72% for **22**.

An alternative acylation method described by Commercon[8] was then applied which utilizes acid **15** in a DCC-DMAP coupling procedure; however after acid **15** and **12** were coupled, deprotection of the Boc group with acid led to a number of sideproducts.[9] Clearly these new molecules were not as stable as their oxygenated precursors, and in order to avoid these problems we prepared the corresponding carbobenzyloxy(Cbz) analog **16** of the aforementioned sidechain so as to be able to both deprotect and reacylate the C-3' amine under practically neutral

conditions. This route proceeded smoothly in that sidechain **16** coupled with **12** producing **17** in 82% yield. After hydrogenolysis of **17**, the mixture was directly filtered and quenched with excess benzoic anhydride to afford the desired 7-deoxy-9-deoxotaxol **18** in 74% yield. Sidechain **16** has also been used with other systems and appears to have general utility for the construction of taxane analogs under mild conditions.

Treatment of **13** with TCDI afforded the C-10 thiocarbonylimidazolide **19**, and this product was deoxygenated as above to give the unique C-7,9,10 defunctionalized intermediate **20**. Sidechain **16** cleanly added at C-13 as above to produce intermediate **21**.[10] Application of the one-pot procedure produced the desired 10-desacetoxy-7-deoxy-9-deoxotaxol (**22**) in 72% yield.

It was interesting to note that no loss of *in vitro* cytotoxicity was exhibited by the 9-deoxo analog, **9** against several tumor cell lines and, little if any loss in activity was shown by 7-deoxy-9-deoxotaxol (**18**). Although ten-fold less active, even trideoxy compound **22** suggests the relative unimportance of the C-7 - C-10 functionalities. Further efforts toward understanding the function vs. activity requirements of the taxane antitumor agents are ongoing.

Table 1. *In vitro* tumor cell cytotoxicity (IC_{50} μg/mL)[a]

	Tumor Cell Lines[b]			
Compound	A549	HT-29	B16F10	P388
9	0.003	0.0022	0.0018	0.0055
18	0.0045	0.0045	0.0047	0.009
22	0.033	0.03	0.031	0.057
Taxol	0.0034	0.0027	0.0041	0.009

[a] Determined by MTT-colorimetric microtiter assay;[11] [b] A549 (human breast cancer), HT-29 (human colon carcinoma), B16F10 (mouse melanoma), P388 (mouse leukemia).

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7. All compounds were fully characterized by ^1H NMR and mass specral data. Compounds **9**, **18**, and **22** were characterized by elemental analyses, along with COSY, ^{13}C NMR, and heteronuclear coupling experiments.
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9. The reaction of **15** and **20** by this method also proceeded poorly affording sideproducts in both the coupling procedure and the deprotection steps.
10. X-ray data for compound **21** were obtained through recrystallization from methanol.
11. IC_{50} is reported as μg/mL concentration of agent which inhibits proliferation of tumor cell growth measured by colorimetry as in T. Mosmann. *J. Immunol. Meth.* **1983**, *65*, 55.

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