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Stereospecific synthesis of the major human metabolite of paclitaxel

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Abstract

The stereospecific synthesis of 6- α -hydroxy paclitaxel **10**, the major human metabolite of paclitaxel, is described. The 6,7- α -diol **4**, obtained from paclitaxel, is converted to the 6,7- β -cyclic sulfate followed by nitrate addition and reduction to afford the title compound. © 2000 Elsevier Science Ltd. All rights reserved.

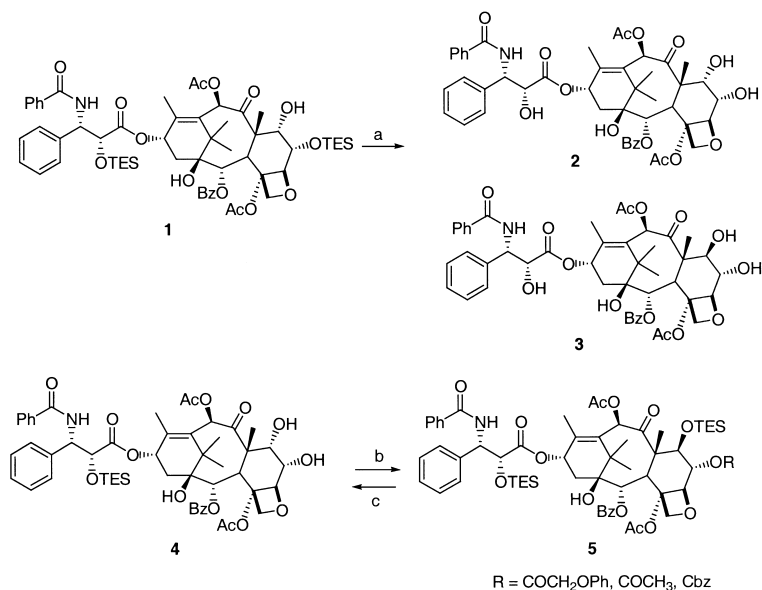
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The expanding clinical use of TAXOL[®] in cancer chemotherapy has fueled an aggressive search within the medicinal chemistry community for second-generation taxanes with improved safety, efficacy, and pharmacokinetics. We required a supply of 6- α -hydroxy paclitaxel **10**, the major human metabolite of paclitaxel,¹ to validate our in vitro assays for the human metabolism of paclitaxel and to evaluate analogs for improved metabolic stability.

Initially, we focused on the epimerization of the silylated α -diol **1** (**4**, TESCl, imidazole, CH₂Cl₂) (Scheme 1). Treatment with KHMDS at 0°C gave a mixture of epimers at C-7, which could not readily be separated. The mixture was then deprotected to give the desired 6- α -hydroxy paclitaxel **3** in 9% yield with 26% of the deprotected α -diol **2**. Due to the low yield of product and poor recovery of **2**, we did not pursue a base-induced epimerization of this substrate. Kingston² has reported the epimerization of the 2'-OTBS ether derivative of diol **2** using DBU to obtain the 2'-OTBS 6- α -hydroxy paclitaxel in 15% yield along with recovered starting diol.

Alternatively, we found that if the 6- α -hydroxyl group of **4** was protected as a phenoxyacetate or acetate, a silylative epimerization could be affected using TESCl and imidazole at elevated temperatures to afford derivatives **5**. This process is likely driven by the fact that the C-7- α hydroxyl is too hindered to react with silylating agents so that any epimerization is quickly trapped with silyl chloride. Various attempts to remove the esters (K₂CO₃, MeOH; KCN, MeOH; Ti(OEt)₄, EtOH) from **5** resulted in removal of both the protecting group and silyl group and re-epimerization

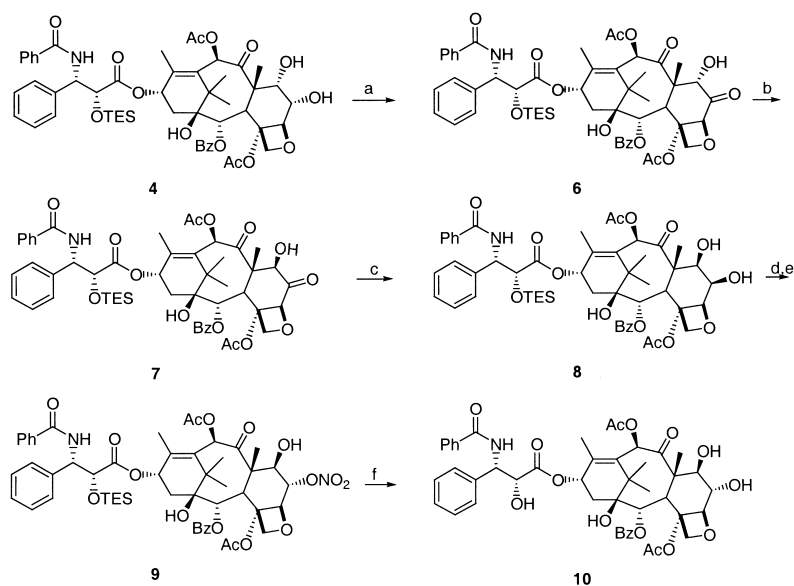
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Scheme 1. *Reagents and conditions:* (a) KHMDS (1.3×), THF 0°C to rt; 1N HCl, CH₃CN 0°C; (b) RCOCl, Et₃N, CH₂Cl₂; TESCl, imidazole, DMF 65°C; (c) K₂CO₃, MeOH; or KCN, MeOH; or Ti(OEt)₄, EtOH; or H₂, Pd-C, MeOH

back to the 2'-O-TES- α -diol **4**. The C-6-hydroxyl group could be protected with a TES group but silylative epimerization yielded only recovered starting material. The C-6 hydroxyl could be protected as the Cbz derivative and C-7 hydroxyl group epimerized and silylated but upon removal of the Cbz group the starting diol was again obtained. Given the difficulty of effectively epimerizing the C-7-hydroxyl group, we opted for an alternative synthetic route which could process the gram quantities our studies required and possibly provide access to other C-6- α analogs.³

Our strategy then turned to conversion of the α -diol **4** to the C-6 ketone (Scheme 2). Several oxidants were effective at oxidizing the C-6 hydroxyl (TPAP, NMO; Jones; Bu₂SnO, Br₂; 4-acetoxyl-TEMPO, pTsOH) but oxidation with catalytic 4-benzoyloxy-TEMPO and bleach⁴ proved to be optimal. The crude ketone **6** was a single isomer but upon silica gel chromatography a mixture of **6** and the 7-epimerized ketone **7** was evident. Epimerization of the 7-hydroxyl could be driven simply by stirring crude **6** in methylene chloride with an equal weight of silica gel. Once the ketone **7** was obtained, we envisioned a directed reduction using sodium triacetoxylborohydride to provide the metabolite. In the event, reduction provided only the β -diol **8**. Other reducing reagents provided varying mixtures of diols favoring the β -diol (NaBH₄, Dibal). The facial selectivity obtained in this reduction arises from the pseudo-equatorial orientation of the C-7 hydroxyl resulting in hydride delivery from the more accessible α -face. In practice, the silica gel was filtered off and the crude ketone reduced with sodium triacetoxylborohydride in acetic acid/acetonitrile to give the 6,7- β -diol **8** in 75% yield from **1** without purification of the intermediates. The high yield of this three-step process, and the ease with which this process is scaled up, makes this longer route a preferable one for preparing large amounts of the metabolite. The cyclic sulfate was prepared according to the method of Sharpless⁵ and opened with tetrabutylammonium nitrate⁶ at the 6-position. Hydrolysis of the sulfate afforded nitrate **9**. Hydrogenolysis of the nitrate provided **10**, which was identical to 6- α -hydroxy paclitaxel by 500 MHz NMR.¹ Incubation of paclitaxel with a human liver S9 preparation provided material identical to **10** by HPLC.



Scheme 2. *Reagents and conditions:* (a) 4-BzO-TEMPO (2%), KBr, Chlorox[®]; (b) silica gel, CH₂Cl₂; (c) Na(OAc)₃BH, HOAc, CH₃CN (75% overall yield for a–c); (d) SOCl₂, Et₃N; NaIO₄, RuCl₃, CCl₄/CH₃CN/H₂O (77%); (e) Bu₄NNO₃, PhMe, 100°C (76%); (f) H₂, Pd/C, MeOH (85%)

In conclusion, we have presented a stereospecific synthesis of 6- α -hydroxy paclitaxel that quickly inverts 6,7- α -diol **1** to the β -diol **8**. The 6- α -hydroxyl can then be introduced via an opening of the 6,7- β -cyclic sulfate.

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