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Stereospecific synthesis of the major human metabolite of paclitaxel

Mark D. Wittman,* John F. Kadow and Dolatrai M. Vyas

Bristol-Myers Squibb Pharmaceutical Research Institute, Division of Chemistry, PO Box 5100, Wallingford, CT 06492-7660, USA

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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.

Keywords: taxoids; diols; oxidation; nitrates; inversion reactions; metabolites.

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, CH_2Cl_2) (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. Kingston[2] 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 (K_2CO_3, MeOH; KCN, MeOH; $Ti(OEt)_4$, EtOH) from **5** resulted in removal of both the protecting group and silyl group and re-epimerization

* Corresponding author.

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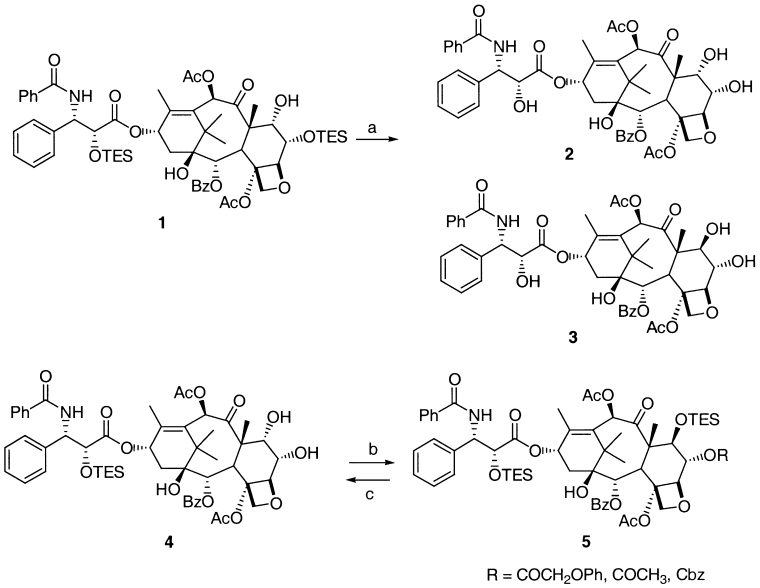
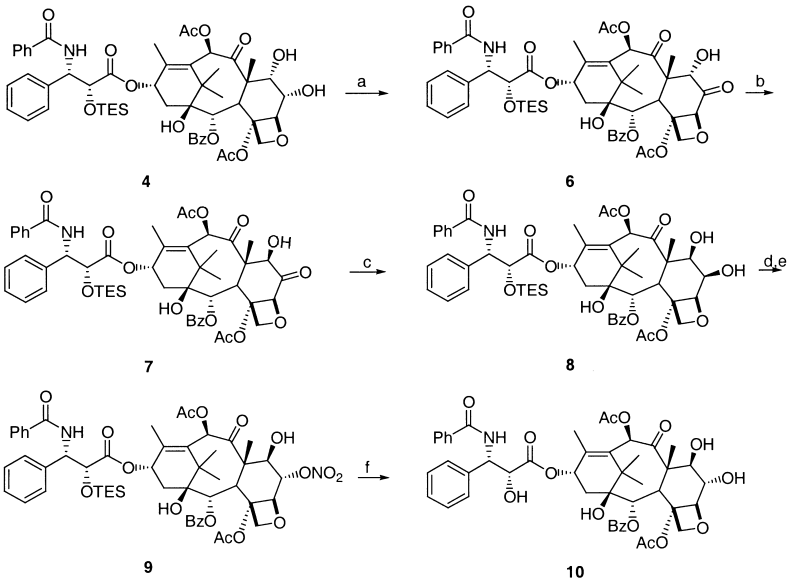


Scheme 1. *Reagents and conditions*: (a) KHMDS (1.3×), THF 0°C to rt; 1N HCl, CH_3CN 0°C; (b) RCOCl, Et_3N, CH_2Cl_2; TESCl, imidazole, DMF 65°C; (c) K_2CO_3, MeOH; or KCN, MeOH; or $Ti(OEt)_4$, EtOH; or H_2, Pd–C, MeOH

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; Bu_2SnO, Br_2; 4-acetoxy-TEMPO, pTsOH) but oxidation with catalytic 4-benzoyloxy-TEMPO and bleach[4] 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 triacetoxyborohydride 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 ($NaBH_4$, Dibal). The facial selectivity obtained in this reduction arises from the pseudo-equatoral 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 triacetoxyborohydride 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 Sharpless[5] and opened with tetrabutylammonium nitrate[6] 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, CH_2Cl_2; (c) $Na(OAc)_3BH$, HOAc, CH_3CN (75% overall yield for a–c); (d) $SOCl_2$, Et_3N; $NaIO_4$, $RuCl_3$, $CCl_4/CH_3CN/H_2O$ (77%); (e) Bu_4NNO_3, PhMe, 100°C (76%); (f) H_2, 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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References

1. Harris, J. W.; Katki, A.; Anderson, L. W.; Chmurny, G. N.; Paukstelis, J. V.; Collins, J. M. *J. Med. Chem.* **1994**, *37*, 706–709.
2. Yuan, H.; Kingston, D. G. I. *Tetrahedron Lett.* **1998**, *39*, 4967–4970.
3. The use of this chemistry to provide C-6 derivatives will be presented in due course.
4. Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559–2562.
5. Gao, Y.; Sharpless, K. B. *J. Am Chem. Soc.* **1988**, *110*, 7538–7539.
6. Cainelli, G.; Manescalchi, F.; Martelli, G.; Panunzio, M.; Plessi, L. *Tetrahedron Lett.* **1985**, *26*, 3369–3372.