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Crystallographic Determination of the Stereochemistry of C-6,7 Epoxy Paclitaxel

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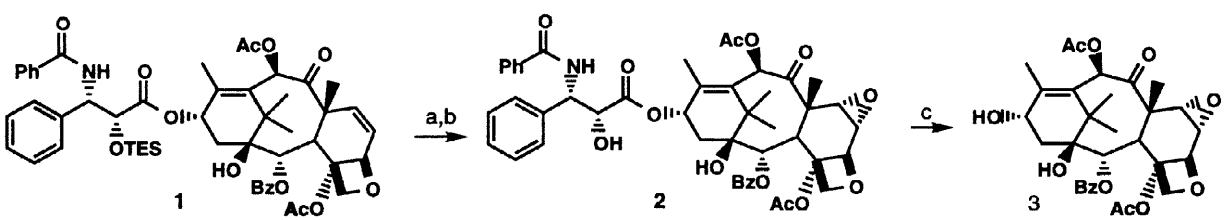
Abstract: The Stereochemistry of C-6,7 epoxy paclitaxel was determined by single crystal X-ray analysis of the baccatin derivative to be 6α, 7α. This finding corrects the structure reported by Kingston et al based on NOE data and corrects the discrepancy reported for facial selectivity of the reaction of osmium tetroxide and dimethyldioxirane with the C-6,7 olefin of paclitaxel.

Paclitaxel (the active constituent of TAXOL®), the diterpenoid natural product isolated from *Taxus brevifolia* in 1971 by Wani and Wall[1] continues to be an attractive target for synthetic and medicinal chemical research. We became interested in the C-6,7 epoxide reported by Roth[2] and Kingston[3] as a potential intermediate for analog synthesis. However, the stereochemistry of this epoxide remains disputed. Kingston used NOE data to assign the β-stereochemistry to the epoxide assuming that dimethyldioxirane attacks the C-6,7 olefin from the sterically less hindered β-face yet, osmium tetroxide reacts with the same olefin via the α-face.[3,4] Botta et al[5] also prepared the C-6,7 epoxide and performed a NOESY experiment that did not confirm the findings of Kingston. These authors suggest that NOE experiments are not definitive due to the similar geometry of both epoxides. We required a crystalline derivative for single crystal X-ray analysis to resolve the epoxide stereochemistry. We felt that removal of the sidechain of the epoxide would be the best approach based on our experience with other taxanes.

The 2'-O-TES-C-6,7 olefin, **1**, was prepared using a modification of the procedure described by Johnson.[6] The olefin was dissolved in a mixture of trifluoroacetone, water and acetonitrile at 0°C and treated with OXONE®[7] to give 2'-O-TES-C-6,7 epoxide which was deprotected with 1N HCl to give epoxide **2** in 88% overall yield.[8] This modified procedure for epoxidation of the C-6,7 olefin avoids the cumbersome preparation of an acetone solution of dimethyldioxirane and yields an epoxide identical to that obtained from treatment with dimethyldioxirane. Cleavage of the sidechain with Bu_4NBH_4 gave the epoxy baccatin in 92% yield (scheme I).

Scheme I



a) $CF_3C(O)CH_3$, $NaHCO_3$, Oxone®, CH_3CN/H_2O; b) 1N HCl,CH_3CN, 0°C (88%)
c) Bu_4NBH_4, MeOH(2%)/CH_2Cl_2 (92%)

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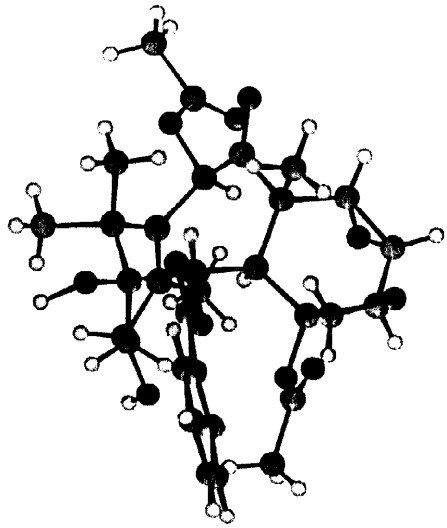
Recrystallization of epoxide **3** from methanol afforded thick colorless plates as a 1:1 methanol solvate. From the crystal structure the epoxide stereochemistry was determined to be 6α, 7α (see figure I). This is in agreement with the structure published by Roth.[2] This is consistent with epoxidation of the olefin from the same face as observed with OsO_4[3,4] ,opposite the allylic ether.[9] The α-face of olefin **1** is sterically least hindered since the β-face is blocked by both the oxetane ring and the C-19 methyl group (see figure I). Finally, we have developed an alternate procedure for synthesis of the α-epoxide on large scale which avoids the necessity to prepare and distill dimethyldioxirane.

Figure I. X-ray Structure of Epoxide 3
(Oxygen Atoms Are Represented In Darker Shading)



References and Notes

TAXOL® is the registered trademark of Bristol-Myers Squibb Company for paclitaxel. X-ray Crystallography: Final atomic coordinates have been deposited in the Cambridge Crystallographic Database. Colorless crystals grown from methanol are Orthorhombic, space group *P212121*, a = 9.4137(7), b = 12.5100(7), c = 25.565(1) Å, V = 3010.7(3) $Å^3$, Z = 4, dx = 1.250 g cm^{-3}. Full-matrix least-squares refinements gave $R(F) = 0.054$, $wR(F) = 0.050$ for 391 parameters and 2758 reflections with $I \geq 3s(I)$.

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