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Highly regio- and stereospecific hydroxylation of C-1 position of 2-deacetoxytaxinine J derivative with DMDO

Tohru Horiguchi, Qian Cheng and Takayuki Oritani *

Laboratory of Applied Bioorganic Chemistry, Graduate School of Agricultural Science, Tohoku University, 1-1 Tsutsumidori-Amamiyamachi, Aoba-ku, Sendai 981, Japan

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Abstract

A simple chemical oxidation of 2-deacetoxytaxinine J derivative **3** using an excess of dimethyldioxirane (DMDO) results in a highly regio- and stereospecific hydroxylation of the C-1 position to afford the 1β-hydroxy α-4(20)-epoxide **6** and 1β-hydroxy β-4(20)-epoxide **7**. A plausible mechanism of this reaction via 'insertion' is proposed.

Keywords: taxoids; dioxiranes; hydroxylation; regiospecificity; stereospecificity; epoxides; epoxidation.

Currently, diterpenoid paclitaxel[1] (Taxol®, **1a**) and docetaxel[2] (Taxotere®, **1b**) are regarded as powerful therapeutic drugs for cancer chemotherapy. Both compounds exhibit potent antitumor activity against various cancers that have been uneffectively treated by existing chemotherapeutic drugs,[2,3] and both have been approved by the FDA for the treatment of advanced ovarian cancer and breast cancer. Paclitaxel was also approved for the second-line treatment of AIDS-related Kaposi's sarcoma in 1997.[4] Recent studies have shown that treatment for various types of advanced solid cancers with paclitaxel and docetaxel often results in the emergence of multi-drug resistance (MDR). This is mainly caused by the over-induction of P-glycoprotein.[5] Therefore, it is important to explore new taxoids either with improved activity against various classes of tumors, especially against drug-resistant human cancers or as functional inhibitors of the P-glycoprotein. In this letter, we thus report that hydroxylation of the C-1 position of 2-deacetoxytaxinine J derivative **3** has been successfully achieved by a simple chemical oxidation using dimethyldioxirane (DMDO)[6] leading to the 1β-hydroxy α-4(20)-epoxide **6** and 1β-hydroxy β-4(20)-epoxide **7** in our ongoing chemical conversions[7] of natural taxoids available from Japanese yew for new taxoid anticancer agents for clinical use.

* Corresponding author. Tel/fax: +81-22-717-8783; e-mail: oritani@biochem.tohoku.ac.jp (T. Oritani)

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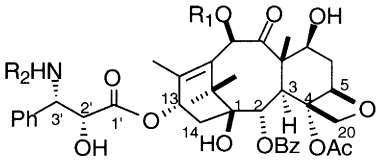
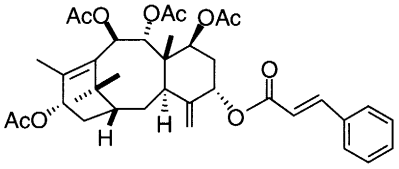
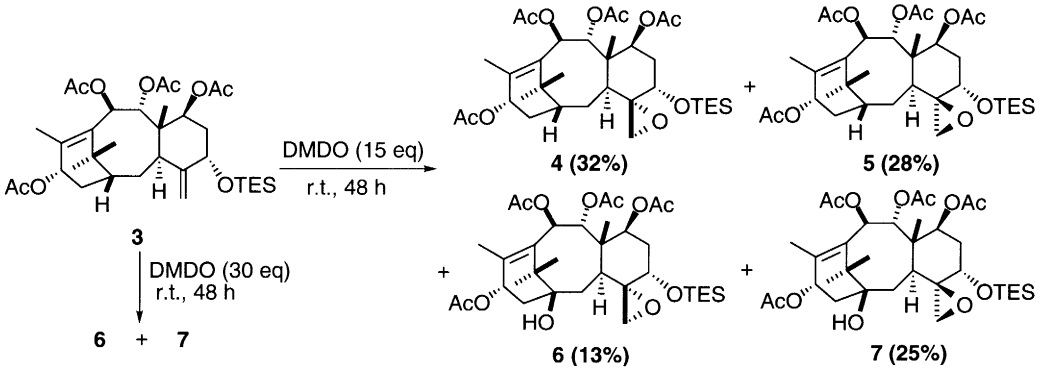


1a: R_1 = Ac, R_2 = Bz, Paclitaxel
1b: R_1 = H, R_2 = Boc, Docetaxol



2: 2-Deacetoxytaxinine J

The 2-deacetoxytaxinine J **2**,[8] which is a natural taxoid isolated from the Japanese yew *Taxus cuspidata*, shows no cardiac toxicity,[9] but might thus serve as an important starting material for the synthesis of new functional inhibitors of the P-glycoprotein. Treatment of **2** with hydroxyamine hydrochloride[10] in ethanol under reflux followed by the protection of 5-hydroxy group with chlorotriethylsilane gave the protected taxoid **3**. The epoxidations of taxinine derivatives leading to 4(20)-epoxides using DMDO (1.8 equiv.) within the stereoselectivity of the α:β ratio in a range from 99:1 to 1:4 have been reported.[11] However, it was found that treatment of **3** with a large excess of DMDO (15 equiv.) in CH_2Cl_2 at room temperature for 48 h afforded the α-4(20)-epoxide **4** and β-4(20)-epoxide **5** in 60% yield (α:β=1.1:1), and the unexpected two more polar products **6** and **7** in 38% yield which were later determined to be the 1β-hydroxy α-4(20)-epoxide and 1β-hydroxy β-4(20)-epoxide,[12] respectively (Scheme 1). While treatment of **3** with 30 equiv. of DMDO under similar conditions gave only **6** and **7** in 90% yield as the reaction products. Additionally, the compounds **4** and **5** could be further converted completely into **6** and **7**, respectively, using 25–30 equiv. of DMDO.



Scheme 1.

The structures and stereochemistries of **4**–**7** were determined by their NMR data including 2D NMR experiments. The NOESY correlations of H-20a to H_2-2 and H_3-19, plus H-20b to H-5β and H-6β were observed in **4** demonstrating the 4(20)-epoxide moiety which possesses the α-orientation. Whereas the β-orientation for the 4(20)-epoxide moiety of **5** was established by the NOESY correlations of H-20a to H-14α. In comparison to the NMR data of **4**, those of **6** displayed high similar structural signals to **4** except where both H_2-14 showed the doublet–doublet signals at δ_H 2.38 (J=14.6, 9.5 Hz) and δ_H 1.86 (J=14.6, 5.3 Hz), respectively, and a new downfield quaternary carbon (C-1) resonanced at δ_c 77.0 (s), attributed to the presence of a hydroxy group located at C-1. This was substantiated by IR absorption at 3400 cm^{-1} and HMRS (FAB) giving the molecular formula as $C_{34}H_{54}O_{11}Si$ for $(M+Na)^+$, calcd: 689.3329; found: 689.3326. Fortunately, the similar assignment of a hydroxyl group located at C-1 was obtained by comparisons of the NMR data of **7** with those of **5** and **6**. The β-orientation of the 1-hydroxyl group for **6** and **7** was established by NOESY studies in which both compounds showed the absence of NOESY correlations of H-2β to H-14β, and H-3α to H-14α.[13]

Formation of 1β-hydroxy 4(20)-epoxides **6** and **7** may be explained via a known 'insertion' of an *O*-atom into an 'unactivated' C–H bond of saturated hydrocarbon as oxygenations of alkanes by metalloporphyrins[14] or by ozone[15] (Fig. 1). This insertion reaction is proposed to involve a transition state I, which might have an appreciable diradical character that leads to the formation of alcohol and it is mediated by caged radical-pairs II; then, in-cage oxidation would lead to the production of alcohols.[16] While the dioxirane O–O bond is being broken, significant widening of the O–C–O angle from 60° to nearly 107° occurs, so that tertiary selectivity asymmetry might serve to relax the energy requirements of the *O*-atom insertion.[17] According to this sequence, the high stereoselectivity recorded might be accommodated, provided one makes the 'assumption' that an in-cage collapse of the radical pair to products occurs faster than the loss of configuration of the caged carbon radical. This stereochemistry of *O*-atom insertion reaction was supported by the regio- and stereospecific hydroxylation of taxoid **3** using DMDO to afford 1β-hydroxy 4(20)-epoxides **6** and **7** with complete retention of configuration. It is thought that highly regioselective hydroxylation at C-1 is more predominant at C-3 in **3**, attributed to a large steric hindrance at C-3 for an optimum stereoalignment of dioxirane attack owing to the convex shape of the taxane skeleton. In fact, the high regioselectivities of tertiary versus secondary and the complete stereospecificities with retention displayed in the *O*-atom insertion with dioxiranes have been reported.[18]

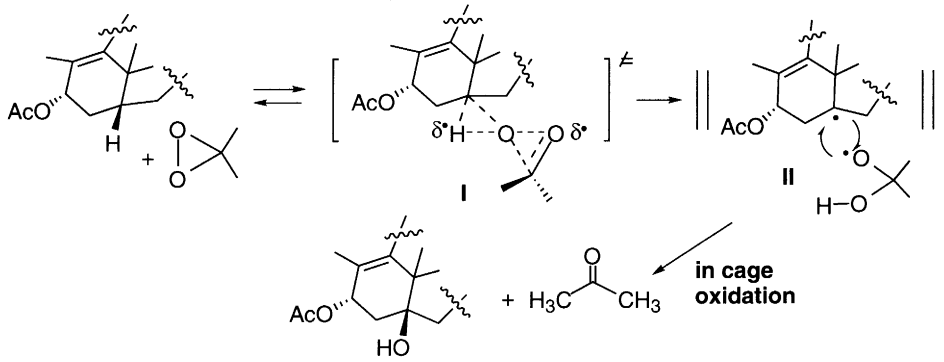


Fig. 1. The proposed mechanism of O-atom insertion reaction of taxoid **3** leads to **6** and **7**

Although a selective microbial hydroxylation of taxoid has been recently reported,[19] this microbial enzymatic reaction led to the hydroxylations at the C-1 and C-14 positions to afford the two compounds, 1β-hydroxy and 14β-hydroxy derivatives in a 1.5:1 ratio as well as A-ring contracted alcohol. To our knowledge, the above-described high regio- and stereospecific hydroxylation leading to only 1β-hydroxy with dimethyldioxirane is the first example to date of the introduction of the hydroxy group at C-1 in the taxoid series by a chemical method. It is worthy to note that this chemistry will be applied for the semisynthesis of biologically active 1β-hydroxy taxoids from a lot of 1β-hydrotaxoids contained in most of the *Taxus* species. These applications are in progress with encouraging results by our group.

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12. Selected spectroscopic data of **6** and **7** are as follows. 1β-OH-α-4(20)-epoxide **6**: $[\alpha]_D^{23}$ +27.4 (*c* 0.12, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.24 (d, 1H, *J*=11.2 Hz), 5.90 (d, 1H, *J*=11.2 Hz), 5.91 (m, 1H), 5.64 (dd, 1H, *J*=11.7, 4.8 Hz), 3.35 (brt, 1H), 2.77 (d, 1H, *J*=6.4 Hz), 2.56 (d, 1H, *J*=4.2 Hz), 2.55 (d, 1H, *J*=4.2 Hz), 2.38 (dd, 1H, *J*=14.6, 9.5 Hz), 2.15 (s, 3H), 2.14 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H), 1.99 (m, 1H), 1.97 (s, 3H), 1.86 (dd, 1H, *J*=14.6, 5.3 Hz), 1.84 (m, 1H), 1.63 (m, 1H), 1.59 (s, 3H), 1.23 (s, 3H), 1.10–0.94 (m, 10H), 0.87 (s, 3H), 0.73–0.63 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.5 (s), 171.1 (s), 170.4 (s), 169.8 (s), 141.1 (s), 134.0 (s), 77.0 (s), 76.9 (d), 73.0 (d), 71.9 (d), 71.4 (s), 70.1 (s), 60.0 (s), 48.8 (t), 47.6 (s), 44.8 (s), 41.1 (t), 37.5 (t), 36.3 (d), 32.6 (t), 28.0 (q), 23.1 (q), 22.2, 22.1, 21.7, 21.6 (4×q), 15.4 (q), 14.0 (q), 6.9 (q), 4.7 (t). 1β-OH-β-4(20)-epoxide **7**. $[\alpha]_D^{23}$ +53.7 (*c* 2.0, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.19 (d, 1H, *J*=11.2 Hz), 6.07 (m, 1H), 5.87 (d, 1H, *J*=11.2 Hz), 5.59 (dd, 1H, *J*=10.7, 4.6 Hz), 3.34 (t, 1H, *J*=3.4 Hz), 2.85 (d, 1H, *J*=3.6 Hz), 2.69 (dd, 1H, *J*=4.9, 2.2 Hz), 2.48 (dd, 1H, *J*=14.9, 9.5 Hz), 2.43 (d, 1H, *J*=3.6 Hz), 2.12 (s, 6H), 2.07 (s, 3H), 2.04 (s, 3H), 2.02 (m, 1H), 1.98 (s, 3H), 1.73–1.70 (m, 2H), 1.63 (dd, 1H, *J*=14.9, 5.1 Hz), 1.57 (s, 3H), 1.19 (s, 3H), 1.09 (s, 3H), 1.00–0.94 (m, 9H), 0.83 (dd, 1H, *J*=15.4, 2.2 Hz), 0.68–0.60 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.3 (s), 171.1 (s), 170.4 (s), 169.9 (s), 140.7 (s), 135.1 (s), 76.9 (d), 76.5 (s), 73.8 (d), 72.0 (d), 71.5 (s), 70.1 (s), 61.5 (s), 48.6 (t), 47.2 (s), 44.9 (s), 40.6 (t), 37.2 (t), 36.1 (d), 32.4 (t), 28.3 (q), 22.5 (q), 22.1, 22.0, 21.7, 21.6 (4×q), 18.1 (q), 15.7 (s), 6.7 (q), 4.6 (t).
13. The comparisons of the NOE data of **6** and **7** with those of the closely related natural and semisynthetic 1β-OH-taxoids exhibit if the 1-hydroxy is α-orientated; there should be strong NOE relationships between H-2β and H-14β, and between H-3α and H-14α. These are confirmed by the molecular model studies. In fact, to our knowledge, so far all natural and semisynthetic 1-OH taxoids having been reported are β-orientated. In addition, it is unreasonable to think about a very steric 1-α-hydroxyl form in a rigid taxane skeleton by an analysis of molecular model.
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