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Et_2AlCl-Mediated Reaction of α-4(20)-Epoxy-5α-hydroxy Taxinine B

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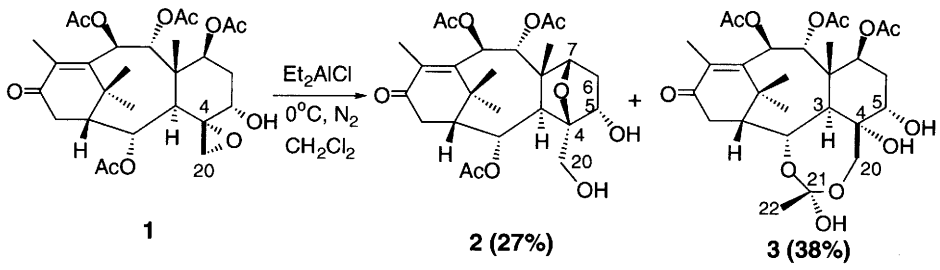
Abstract: An α-4(20)-epoxy-5α-hydroxytaxinine B **1**, when treated with diethylaluminum chloride, underwent reactions involving intramolecular substitution along with deacetylation or addition leading to new rings. Two novel 1-deoxy compounds **2** and **3** were isolated and fully characterized.

Keywords: Antitumour compounds, taxoides, epoxide, diethylaluminum chloride.

The anticancer drug paclitaxel (Taxol®), a diterpenoid isolated from the bark of *Taxus brevifolia*[1], is clinically used in the treatment of ovarian and breast cancers[2]. Since its discovery in the 1960s, particularly in recent years, a large number of studies on chemistry and structure-activity relationship have been carried out and led to the general conclusion that the function groups at C_7, C_9, C_{10}, $C_{11\text{-}12}$ and C_8-CH_3 have modest but often beneficial effects on its biological activity, while the side chain at C13, the ester groups at C_2 and C_4 and the oxetane ring are all essential for biological activity[3]. Alothough the first semisynthesis of 1-deoxypaclitaxel analogs has been reported by Kingston, *et al*[4], the role of the C_1-OH group on biological activity has not been very clear due to the fact that 1-deoxypaclitaxel and its derivatives are difficult to prepare[5]. Thus, chemical conversion of more readily available taxoids from Japanese yew to paclitaxel including 1-deoxypaclitaxel and their analogs is still interesting research area for chemists. In this communication we report two novel 1-deoxy compounds **2** and **3** obtained from α-4(20)-epoxy-5α-hydroxytaxinine B **1** in the presence of diethylaluminum chloride and propose plausible mechanism of its reaction.

Scheme 1



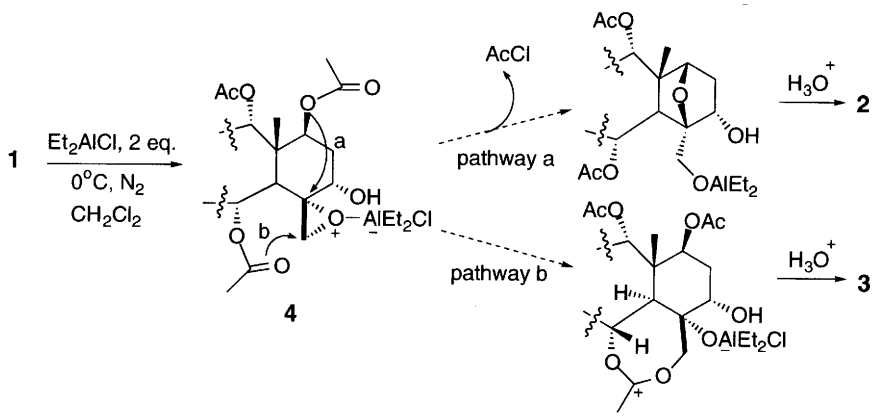
Taxinine B[6], one of the major taxoids isolated from the needles of Japanese *yew Taxus cuspidata*, which can be converted to 5α-hydroxytaxinine B according to known method[7]. We found that Et_2AlCl-mediated reaction of α-4(20)-epoxy-5α-hydroxytaxinine B **1** derived from 5α-hydroxytaxinine B by epoxidation using *m*-chloroperbenzoic acid[8], in CH_2Cl_2 at 0°C under nitrogen yielded a 4,7-oxygen bridge (**2**, 27%) and a 6/8/6/7 ring system (**3**, 38%), two 1-deoxy compounds[9] (**Scheme 1**). Analysis of the ^1H and ^{13}C NMR spectra of compound **2** indicated the loss of an acetyl group and this was substantiated by EIMS of **2** giving the molecular ion at *m/z* 508 and HREIMS suggesting the molecular formula as $C_{26}H_{36}O_{10}$ for M^+ 508.2276. The ^{13}C NMR and HMQC spectra showed that a tertiary carbon at δ_c 67.15ppm (d) and a quaternary carbon at δ_C 79.07ppm (s) were assigned to C-7 and C-4, respectively by HMBC correlations of H-3 (δ_H 3.37, d, J=5.5Hz), H-5(δ_H 3.84, br dd) and H-6 (δ_H 2.10, m, 1.83, m) to C-4 and C-7. All above information suggested that the presence of an oxygen-bridge was fused between C-4 and C-7 by HMBC correlation of H-7 (δ_H 4.32, dd, J=5/4Hz) to C-4. Morever, the NMR data revealed the a hydroxymethylene group (δ_H 3.81, d, J=11.2Hz and 4.24, d, J=11.2Hz, H_2-20; δ_c 63.47, t, C-20) was connected at C-4 by HMBC correlations of H-3 and H-5 to C-20 and H_2-20 to C-4. The β-orientation of the oxyen-bridge was deduced by NOESY correlations of H-6α to H-10 and H-3 and the absence of NOE relationship between H-5 and H-2 as well as between H-6β and CH_3-19[10]. Compound **3** was found to have a molecular formula $C_{28}H_{40}O_{12}$ by HRFABMS for MH^+ 569.2567(Δ1.2mmu). The ^1H NMR data showed two protons at (δ_H 3.51, d, J=9Hz and 3.72, d, J=9Hz, H_2-20) suggesting an oxymethylene group was connected to C-4 (**(**δ_C 78.79, s). This was confirmde by HMBC correlations of: H-3 (**(**δ_H 3.04, d, J=5Hz) and H-5 (**(**δ_H 4.05, brt) to C-20 (δ_C 74.24, t) and C-4, and H_2-20 to C-3 (**(**δ_C 43.59, d), C-4, and C-5 (**(**δ_C 70.10, d). In addition, the NMR spectra exhibited only three acetyl groups and a new singlet of quaternary carbon at downfield (**(**δ_C 120.17, s, C-21), attributable to the carbon bearing three oxygen substituents which was further confirmed by HMBC correlations of H-2 (**(**δ_H 5.18, dd, J=5/2.4Hz), H_2-20 and CH_3-22 (**(**δ_H 1.65, s) to C-21. The above observations indicated the presence of a seven-membered ring which was fused between C-2 and C-4. Finally the NOESY correlations of H-20a to H-2, CH_3-19 and H-20b to H-6β including CH_3-22 to H-2 indicated the oxymethylene group at C-4 and CH_3-22 both processing the β-orientation.

Plausible mechanism of Et_2AlCl-mediated reaction of compound **1** is shown in **Figure 1**. Formation of **2** and **3** from **1** can be explained *via* intramolecular substitution and addition, respectively. The most likely first step is the complexation of the Lewis acid with the α-epoxide to give **4**, then the oxygen at C-7 is positioned for nucleophilic attack at C-4 from β-face followed by loss of acetyl group (pathway a) leading to the oxygen-bridged precursor to compound **2**. Altematively, compound **3** can arise easily from intermediate **4** *via* nucleophilic attack at C-20 by the oxygen of the acetyl group at C-2 generating a seven-membered ring bearing the carbocation at C-21 (pathway b), to be finally hydroxylated upon aqueous workup conditions.

In summary, two 1-deoxy compounds have obtained from α-(40)-epoxy-5α-hydroxytaxinine B in the presence of diethylaluminum chloride and plausible mechanism of Et_2AlCl-mediated reaction has been proposed. Furthermore, it

is noted that compound **2** is the first sample bearing the oxygen-bridge fused between C-4 and C-7 in this taxoid series.

Figure 1. Plausible mechanism of Et2AlCl-mediated reaction of compound **1**



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9. **Experimental procedure of Et_2AlCl-mediated reaction and selected spectral data as follows**: To an ice-cooled solution of α-4(20)-epoxy-5α-hydroxytaxinine B **1** (55 mg, 0.1 mmol) in dry CH_2Cl_2 (2 ml), was added Et_2AlCl 1.0M solution in hexanes (0.2 ml, 0.2 mmol) at 0°C under nitrogen. The reaction mixture was stirred for 0.5 h and then the saturated aqueous NH_4Cl (0.5 ml) was added. The resulting mixture was extracted with $CHCl_3$ and dried

over $MgSO_4$. After removal of solvent, the residue was chromatographed on siclica gel (EtOAc:hexane=2:1) to give compounds **2** (14 mg, 27%) and **3** (21 mg, 38%). **Compound 2:** $[\alpha]^{22}_D$ +57 (c 0.6, CHC_{l3}). UV λ_{max}(lgε) =243 nm (3.65). ^{1}H-NMR(600MHz, CDC_{l3}) δ_H: 1.13 (s, 3H, CH_3-19), 1.21(s, 3H, CH_3-17), 1.70(s, 3H, CH_3-16), 1.83(m, 1H, H-6), 2.05(s, 3H, Ac), 2.08(s, 3H, Ac), 2.10(m, 1H, H-6), 2.15(s, 3H, Ac), 2.17(dd, 1H, J=6.7, 2.2Hz, H-1), 2.26(s, 3H, CH_3-18), 2.78(dd, 1H, J=19.5, 6.7Hz, H-14β), 3.24(d, 1H, J=19.5Hz, H-14α), 3.37(d, 1H, J=5.5Hz, H-3), 3.81(d, 1H, J=11.2Hz, H-20), 3.84(brdd, 1H, H-5), 4.24(d, 1H, J=11.2Hz, H-20), 4.32(dd, 1H, J=5, 4Hz, H-7), 5.76(dd, 1H, J=5.5, 2.2Hz, H-2), 5.94(d, 1H, J=11Hz, H-9), 6.21(d, 1H, J=11Hz, H-10). ^{13}C-NMR(150MHz, CDC_{l3}) δ_c: 13.45(q, C-19), 14.52(q, C-18), 20.77, 20.92, 21.47(3×q, 3×Ac), 25.47(q, C-16), 33.27(t, C-6), 36.47(t, C-14), 36.75(q, C-17), 38.56(s, C-15), 45.69(d, C-3), 48.13(d, C-1), 49.24(s, C-8), 63.42(t, C-20), 67.15(d, C-7), 70.05(d, C-5), 70.94(d, C-2), 72.48(d, C-10), 74.32(d, C-9), 79.07(s, C-4), 140.02(s, C-12), 150.15(s, C-11), 169.41, 169.84, 170.67(3×s, 3×Ac), 199.86(s, C-13). HREIMS calcd. for $C_{26}H_{36}O_{10}$ (M^+) 508.2306, found 508.2276 (Δ 2.3 mmu). **Compound 3:** $[\alpha]^{22}_D$ +135 (c 0.15, $CHCl_3$). UVλ_{max}(lgε) =239 nm (3.36). ^{1}H-NMR(600MHz, $CDCl_3$) δ_H: 1.01 (s, 3H, CH_3-19), 1.21(s, 3H, CH_3-17), 1.65(s, 3H, CH_3-22), 1.70(m, 1H, H-6), 1.75(s, 3H, CH_3-16), 1.95(m, 1H, H-6), 2.01(s, 3H, Ac), 2.06(s, 3H, Ac), 2.14(s, 3H, Ac), 2.17(dd, 1H, J=6.5, 2.4Hz, H-1), 2.20(s, 3H, CH_3-18), 2.84(dd, 1H, J=19.5, 6.5Hz, H-14β), 3.04(d, 1H, J=5Hz, H-3), 3.12(d, 1H, J=19.5Hz, H-14α), 3.51(d, 1H, J=9Hz, H-20), 3.72(d, 1H, J=9Hz, H-20), 4.05(brt, 1H, H-5), 5.18(dd, 1H, J=5, 2.4Hz, H-2), 5.59(dd, 1H, J=11.5, 5.2Hz, H-7), 5.87(d, 1H, J=11Hz, H-9), 6.24(d, 1H, J=11Hz, H-10). ^{13}C-NMR(150MHz, $CDCl_3$) δ_c: 13.09(q, C-19), 14.15(q, C-18), 20.43, 20.76, 20.92(3×q, 3×Ac), 23.10(q, C-22), 24.86(q, C-16), 31.78(t, C-6), 34.16(q, C-17), 37.42(t, C-14), 38.67(s, C-15), 43.59(d, C-3), 48.02(s, C-8), 48.54(d, C-1), 69.42(d, C-7), 70.10(d, C-5), 72.07(d, C-10), 73.43(d, C-2), 74.24(t, C-20), 75.12(d, C-9), 78.79(s, C-4), 120.17(s, C-21), 140.67(s, C-12), 152.86(s, C-11), 169.23, 169.83, 170.42(3×s, 3×Ac), 199.67(s, C-13). HRFAB-MS calcd. for $C_{28}H_{41}O_{12}$ (MH^+) 569.2595, found 569.2567 (Δ1.2 mmu).

10. Molecular model studies show if the oxygen-bridge is the α-orientation, the molecule should have NOESY correlations of H-5 to H-2 and CH_3-19 as well as H-6β to CH_3-19. However, such correlations were not observed in NOESY experiment of **2**.

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