

## A Highly Regioselective Deacetylation of Taxanes

Meng ZHANG, Da Li YIN\*, Ji Yu GUO, Xiao Tian LIANG

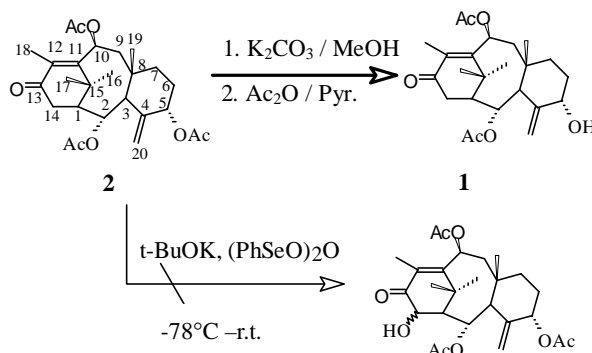
Institute of Materia Medica, Chinese Academy of Medical Sciences &  
Peking Union Medical College, Beijing 100050

**Abstract:** A highly regioselective O-deacetylation of taxanes at C-5 position was accomplished by treatment with *t*-BuOK and a possible mechanism was proposed.

**Keywords:** Paclitaxel, taxane, deacetylation.

Paclitaxel and its semisynthetic analogue, docetaxel, are the most promising antitumour agents available today. SAR studies have revealed that the functionalities at C-1, C-7, C-9 are not important for antitumor activity<sup>1,2</sup>. We have reported the synthetic studies of 1, 7, 9-trideoxytaxol<sup>3</sup>. In this route, compound **1** as a key intermediate was obtained from **2** by total hydrolysis with  $K_2CO_3/MeOH$  and then selective acetylation with  $Ac_2O/Pyridine$ , but in very low yield (**Scheme 1**). Here O-deacetylation of the three acetyl groups of compound **2** with  $K_2CO_3/MeOH$  gave the sequence of C-10 > C-2 > C-5. We have tried to directly remove 5-acetyl group of compound **2** under various conditions including the method of removal of 5-cinnamoyl of taxinine<sup>4</sup>, but all the results were

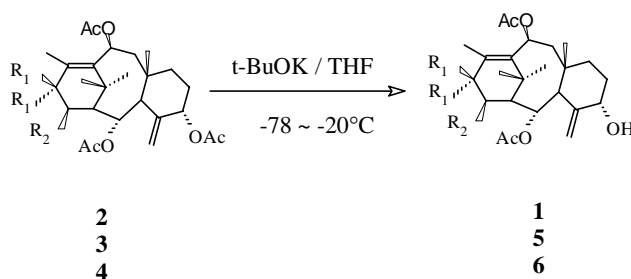
Scheme 1



not satisfactory. When compound **2** was treated with  $t-BuOK/(PhSeO)_2O$ , for introducing hydroxyl group at C-14,<sup>5</sup> It was found that compound **1** was the only product. We doubted if the reagent  $(PhSeO)_2O$  was necessary in this deacetylation reaction.

Thus we treated compound **2** with *t*-BuOK without (PhSeO)<sub>2</sub>O under the same condition, again compound **1** was afforded in high yield. This method could be a new approach for selective deacetylation at C-5, shown in **Scheme 2**<sup>9</sup>.

**Scheme 2**



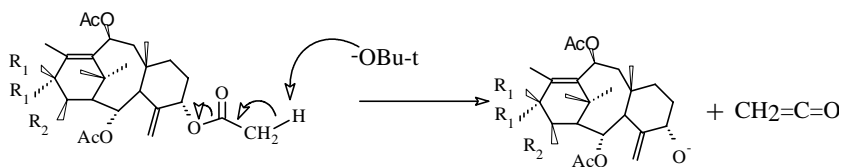
**2, 1:** R<sub>1</sub> = O (carbonyl), R<sub>2</sub> = H; 1 h, 93%

**3, 5:** R<sub>1</sub> = R<sub>2</sub> = H; 40 min., almost quantitative

**4, 6:** R<sub>1</sub> = H, R<sub>2</sub> = OAc; 1 h, 72%

Having successfully performed the selective removal of C-5 acetyl group, we were very interested in studying the possible mechanism. An earlier reference about removal of the C-4 acetyl group with *t*-BuOK in baccatin III had reported<sup>6</sup> that the possible mechanism was an intramolecular transfer of the acetyl group from the C-4 to the C-13 oxygen. We suspected that although the C-13 oxygen of compound **2** was very close to acetyl at C-5, the oxygen of carbonyl or en-2-ol at C-13 as a weak nucleophile was very difficult to remove acetyl at C-5. We reasoned that ketene could be formed under the action of *t*-BuOK during the reaction and the C-13 oxygen did not play any role in the deacetylation at C-5. In order to confirm our supposition, compound **3** and **4** were treated with *t*-BuOK under the same condition. **5** and **6** were obtained in high yields, which indicated the “neighboring group” effect of the C-13 oxygen did not exist. We designed an experiment to detect the possible existence of ketene. When the reaction was proceeded for 5 minutes, aniline (1.5equiv) was added<sup>7</sup>. After the reaction was finished, workup and purification of the crude mixture afforded 5-deacetyl taxanes and acetanilide which was confirmed by <sup>1</sup>HNMR and EIMS. Compound **2**, **3** and **4** gave the same results. Therefore, we proposed that the mechanism of this reaction might be outlined as **Scheme 3**. After the disappearance of starting material EtOAc was added into the reaction solution and the reaction mixture was allowed to stand overnight at room temperature, part of the starting material showed up again. This result indicated that the ester exchange between the 5-O<sup>-</sup> anion and EtOAc proceeded in the presence of *t*-BuOK.

Scheme 3



This proposed mechanism will be further demonstrated in work. The structures of all compounds were confirmed by NMR and MS<sup>8</sup>.

### Acknowledgment

This research work was financially supported by NNSFC.

### References and Notes

1. D. G. I. Kingston, *J. Nat. Prod.*, **2000**, *63*, 726.
2. D. G. I. Kingston, M. D. Choridia, P. G Jagtap, *et al.*, *J. Org. Chem.*, **1999**, *64*, 1814.
3. Meng Zhang, Da Li Yin, Ji Yu Guo, Xiao Tian Liang, *C.C.L.* has been accepted
4. Y. Bathini, R. G. Micetich, M. Daneshtalab, *synth. Commun.*, **1994**, *24*, 1513
5. S. J. Danishefsky, J. J. Masters, W. B. Young, *et al.*, *J. Am. Chem. Soc.*, **1996**, *118*, 2843.
6. A. Datta, L. R. Jayasinghe, G. I. Georg, *J. Org. Chem.*, **1994**, *59*, 4689.
7. A control experiment was accomplished: taxanes were treated with aniline without t-BuOK. No reaction was found in this experiment.
8. Compound **4**, Sinenxan A, a biosynthetic taxane product; Compound **1**, **3** was synthesized according to ref. 3.  
 selected data of other compounds:  
**2**: <sup>1</sup>HNMR (500MHz, CDCl<sub>3</sub>, δ ppm) 6.12 (dd, 1H, J=12Hz, 5.5Hz, H-10), 5.47 (dd, 1H, J=2Hz, 6.5Hz, H-2), 5.09 (s, 1H, H-20), 4.76 (s, 1H, H-20), 4.16 (br.s, 1H, H-5), 3.51 (d, 1H, J=6Hz, H-3), 2.77 (dd, 1H, J=7Hz, 19.5Hz, H-14), 2.44 (dd, 1H, J=12.5Hz, 15Hz, H-9), 2.37 (d, 1H, J=20Hz, H-14), 2.18 (s, 3H, OAc-CH<sub>3</sub>-10), 2.13 (dd, 1H, J=1.7Hz, 6.7Hz, H-1), 2.09 (s, 3H, OAc-CH<sub>3</sub>-2), 2.07 (s, 3H, CH<sub>3</sub>-18), 2.10-2.06 (m, 1H, H-7), 1.73 (m, 3H, 2×H-6, H-9), 1.69 (s, 3H, CH<sub>3</sub>-16), 1.18 (m, 1H, H-7), 1.13 (s, 3H, CH<sub>3</sub>-17), 0.87 (s, 3H, CH<sub>3</sub>-19); <sup>13</sup>CNMR (125MHz, CDCl<sub>3</sub>, δ ppm) 199.93 (13-C=O), 169.97 (OAc-C=O), 169.71 (OAc-C=O), 152.77 (C-20), 147.75 (C-12), 136.80 (C-11), 113.14 (C-4), 76.08 (C-10), 71.11 (C-2), 70.87 (C-5), 49.12 (C-1), 42.86 (C-15), 39.84 (C-8), 39.07 (C-14), 37.95 (C-3), 37.25 (C-6), 36.10 (C-9), 32.95 (C-7), 30.98 (C-17), 24.75 (C-16), 22.45 (C-18), 21.46 (OAc-CH<sub>3</sub>), 21.27 (OAc-CH<sub>3</sub>), 13.85 (C-19); FABMS *m/z* 419.3(M+1).  
**3**: <sup>1</sup>HNMR (500MHz, CDCl<sub>3</sub>, δ ppm) 6.06 (dd, 1H, J=5Hz, 12.3Hz, H-10), 5.38(dd, 1H, J=1.7Hz, 6Hz, H-2), 5.27 (t, 1H, J=3Hz, H-5), 5.25 (s, 1H, H-20), 4.80 (s, 1H, H-20), 3.08 (d, 1H, J=6Hz, H-3), 2.46 (m, 1H, H-13), 2.37 (dd, 1H, J=12Hz, 14.7Hz, H-9), 2.12 (s, 3H, 10-OAc-CH<sub>3</sub>), 2.06 (s, 3H, 18-CH<sub>3</sub>), 2.04 (s, 3H, 2-OAc-CH<sub>3</sub>), 2.03 (s, 3H, 5-OAc-CH<sub>3</sub>), 2.09-1.88 (m, 3H, H-13, H-14, H-7), 1.81 (m, 2H, H-6, H-1), 1.69 (m, 1H, H-14), 1.61 (s, 3H, 16-CH<sub>3</sub>), 1.62-1.58 (m, 1H, H-9), 1.23 (m, 1H, H-7), 1.06 (s, 3H, 17-CH<sub>3</sub>), 0.84 (s, 3H, 19-CH<sub>3</sub>); FABMS *m/z* 447.1(M+1).  
**5**: <sup>1</sup>HNMR (500MHz, CDCl<sub>3</sub>, δ ppm) 6.11 (dd, 1H, J=5.5Hz, 12Hz, H-10), 5.38(d, 1H, J=6Hz, H-2), 5.10 (s, 1H, H-20), 4.80 (s, 1H, H-20), 4.20 (s, 1H, H-5), 3.35 (d, 1H, J=6Hz, H-3), 2.38 (m, 1H, H-13), 2.33 (dd, 1H, J=12Hz, 15Hz, H-9), 2.06 (s, 3H, 10-OAc-CH<sub>3</sub>), 2.05

(s, 3H, 18-CH<sub>3</sub>), 2.04 (s, 3H, 2-OAc-CH<sub>3</sub>), 2.19-2.04 (m, 2H, H-1, H-14), 1.90 (m, 1H, H-6), 1.78-1.65 (m, 4H, H-6, H-7, H-9, H-13, H-14), 1.60 (s, 3H, 16-CH<sub>3</sub>), 1.59 (dd, 1H, J=5.5Hz, 15Hz, H-9), 1.15 (m, 1H, H-7), 1.06 (s, 3H, 17-CH<sub>3</sub>), 0.83 (s, 3H, 19-CH<sub>3</sub>); FABMS *m/z* 405. 1(M+1)

**6:** <sup>1</sup>HNMR (500MHz, CDCl<sub>3</sub>, δ ppm) 6.11 (dd, 1H, J=5Hz, 12Hz, H-10), 5.34(dd, 1H, J=2.3Hz, 6.3Hz, H-2), 5.11 (s, 1H, H-20), 5.04 (dd, 1H, J=4.5Hz, 9.5Hz, H-14), 4.78 (s, 1H, H-20), 4.19 (t, 1H, J=2.7Hz, H-5), 3.21 (d, 1H, J=6Hz, H-3), 2.77 (dd, 1H, J=9.3Hz, 19.3Hz, H-13), 2.36 (dd, 1H, J=4Hz, 19.3Hz, H-13), 2.33 (dd, 1H, J=12Hz, 15Hz, H-9), 2.11 (m, 1H, H-7), 2.08 (s, 3H, 10-OAc-CH<sub>3</sub>), 2.05 (s, 3H, 18-CH<sub>3</sub>), 2.02 (s, 3H, 2-OAc-CH<sub>3</sub>), 1.84 (d, 1H, J=2Hz H-1), 1.73 (m, 2H, H-6), 1.65 (s, 3H, 16-CH<sub>3</sub>), 1.59 (dd, 1H, J=6Hz, 15Hz, H-9), 1.14 (m, 1H, H-7), 1.11 (s, 3H, 17-CH<sub>3</sub>), 0.81 (s, 3H, 19-CH<sub>3</sub>); FABMS *m/z* 463. 2(M+1)

**Acetanilide:** <sup>1</sup>HNMR (300MHz, CDCl<sub>3</sub>, δ ppm) 2.16 (s, 3H, CH<sub>3</sub>), 7.60 (br.s, 1H, NH), 7.52-7.08 (m, 5H, Ph-H); EIMS *m/z* 135 (M<sup>+</sup>), 119, 106, 93 (based peak), 74, 65, 51, 43;

9. Preparation of compound **1**

To a solution of compound **2** (80 mg, 0.1739 mmol) in dry THF (3 mL) was added t-BuOK (78 mg, 0.6956 mmol) at -78°C under N<sub>2</sub>. The reaction mixture was stirred at -20°C for 1 h. The mixture was diluted with EtOAc (20 mL) and poured into saturated NaHCO<sub>3</sub> (5 mL). The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by chromatography (hexane/EtOAc, 4:1), yielding compound **1** (68 mg, 93%)

Received 21 November, 2001