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Reduction of 1- Deoxy -13 – oxotaxanes

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

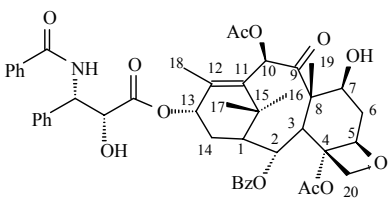
Institute of Materia Medica, Chinese Academy of Medical Science &
Peking Union Medical College, Beijing 100050

Abstract: Reduction of 1-deoxy-13-oxotaxanes has been studied under different reaction conditions. Some interesting reactions were reported.

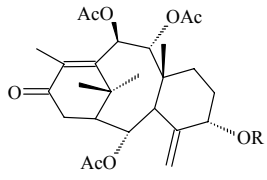
Keywords: Paclitaxel, taxane, reduction.

Numerous reports have described the semisynthesis of paclitaxel and its anologues from different taxoids [1]. However, to the best of our knowledge almost all taxoids have a C-1-hydroxyl. Heretofore, the semisynthesis from taxinine, an abundant natural taxoid lacking of C-1-hydroxyl, has only reached the point of C-13 ketone intermediate [2]. We have also encountered difficulties in reducing C-13 ketone to corresponding α- hydroxy group using the same conditions as in total synthesis of paclitaxel. The possible reason would be that the carbonyl at C-13 position of 1-deoxytaxane is not easy to be reduced toα-hydroxyl under a mild condition without assistance of C-1-hydroxyl [3, 6]. Recently, we have reported sinenxan A was transformed to baccatin III analogue and discover that C-4-hydroxy assist the reduction of C-13-carbonyl of 1-deoxytaxane to get C-13-α-hydroxyl [4]. Here we report some interesting results of C-13-carbonyl to C-13- α- hydroxyl using different reductants.

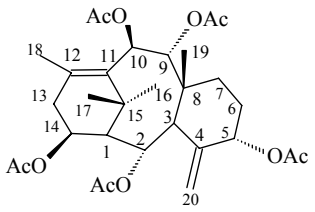
When **1** was treated with K-selectride, an unusual 10-deoxytaxane **2** was obtained [5]. Compared with that of **1**, the ^{1}HNMR spectrum of **2** showed the proton signals of 10-acetyl and H-10 disappeared and the proton signal at C-9 position was changed from δ 2.48 ppm (dd, J = 12, 15 Hz) and δ 1.77 ppm (dd, J = 6, 15.5 Hz) to δ 2.14 ppm (dt, J = 12, 5, 16 Hz)



Paclitaxel



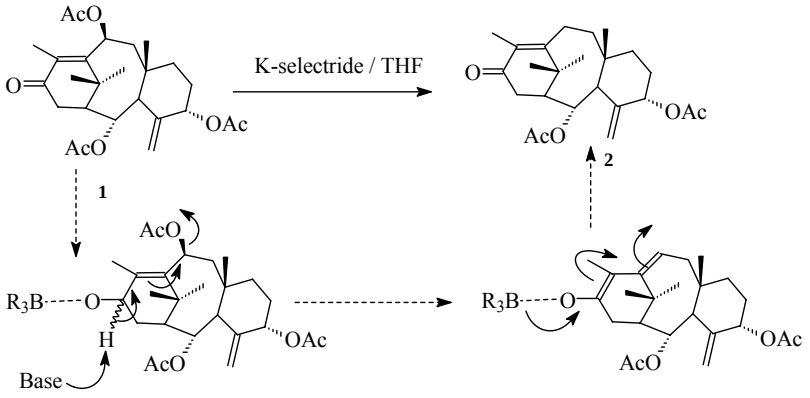
Taxinine



Sineuxan A (SIA)

* E-mail: yindali@imm.ac.cn

Scheme 1



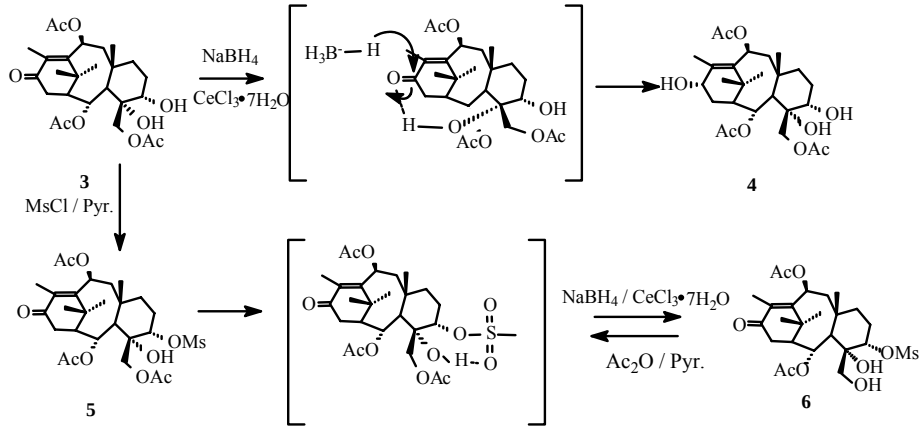
and δ 1.51 ppm (m, J = 5, 15.5 Hz), which were coupled with a group of newly observed peaks at δ 2.91 ppm (dq, J= 5.5, 12, 13.5 Hz) and δ 2.39 ppm (dt, J = 5, 13 Hz), assigned to H-10. Other proton signals did not give an obvious shift. ^{13}CNMR indicates the signal of C-10 and 10-Acetate carbonyl group has been removed away from downfield, the carbonyl signal at C-13 position and double bond signal at C-11 and C-12 was retained. FABMS give a molecular weight of 402 which indicates a deletion of acetoxyl group from its framework. All data confirmed the structure of 10-deoxytaxane **2** (**Scheme 1)**.

The formation of **2** may be explained by **scheme 1**. While 13-oxo of **1** was reduced with K-selectride, the newly formed H-13 was caught by strong base in the solution. Double bond $\Delta^{10,11}$ was formed and the acetoxyl group at C-10 was removed by an electron transfer procedure. After workup, the enol compound was transformed into ketone **2**.

When $NaBH_4$ was employed to reduce the C-13 carbonyl, **3** was successfully converted to **4** by a transannular assistant of C-4-hydroxy [3]. However, when **5** was reduced with $NaBH_4$, a 20-deacetyl product **6** was given [5]. Obviously, the 5-mesyl of **5** forms a hydrogen bond with C-4-hydroxyl so as to break the hydrogen bond between C-13-oxo and C-4-hydroxyl. Thus C-13-oxo of **5** cannot be reduced and excess $NaBH_4$ has enough ability to reductive deacetylation of 20-acetyl after a long reaction time. **(Scheme 2)**

Among the reductants, DIBAH is another choice to get C-13-α-hydroxyl. When **1** was treated with DIBAH, some complex products were shown on TLC which may be caused by the ability of DIBAH to reduce acyl group. Thus **1** was converted into **7** and then treated with DIBAH resulted in **8** [5] as a single product (scheme **3**). ^{1}HNMR shows a new proton signal resonates at δ 4.23 ppm correlated to H-14. NOE spectrum reveals this proton display a strong correlation with H-14, CH_3-17, CH_3-18. These data indicate it is a signal of H-13 with β orientation, which means C-13-α-hydroxyl group was formed.

Scheme 2



Scheme 3

In summary, we have got two methods to reduce C-13-carbonyl of 1-deoxytaxane to C-13- α -hydroxyl, reduction with $NaBH_4$ by a transannular assistant of C-4-hydroxyl and reduction with DIBAH by pre-protection of the other functional groups. We wish our research can offer some help for the study of taxoids chemistry.

Acknowledgment

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References and Notes

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2. T. Horiguchi, T. Oritani, H. Kiyota, *Tetrahydron,* **2003**, *59, 1529*
3. H. Suzuki, M. Sako, K. Hirota, *Chem. Pharm. Bull.*,**1998**, *46, 8*57.
4. M. Zhang, D. L. Yin, J. Y. Guo, X. T. Liang, *Tetrahedron Lett.*, **2002**, *43*, 9425.
5. Compound **1, 3, 4, 5** were synthesized according to reference 4.
   Spectral data of compound **2**: colorless film; FABMS *m/z* 425 (M+Na); ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm) 5.44 (dd, 1H, *J* = 2, 6 Hz, H-2), 5.20 (t, 1H, *J* = 3.5 Hz, H-5), 5.16 (s, 1H, H-20), 4.77 (s, 1H, H-20), 3.28 (d, 1H, *J* = 6 Hz, H-3), 2.91 (dq, 1H, *J* = 5.5, 12.5, 13.5 Hz, H-10), 2.75 (dd, 1H, *J* = 7, 20 Hz, H-14), 2.34 (d, 1H, *J* = 20 Hz, H-14), 2.17 (dd, 1H, *J* = 2, 7 Hz, H-1), 2.13 (hept., 1H, *J* = 5, 12, 16 Hz, H-9), 2.04-2.02 (2s, 6H, 2×OAc-CH_3), 1.99 (br.s,

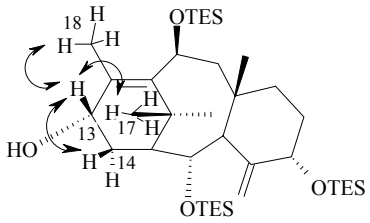
3H, CH_3-18), 1.97-1.91 (m, 1H, H-7), 1.89-1.82 (m, 1H, H-6), 1.72 (m, 1H, H-6), 1.58 (s, 3H, CH_3-16), 1.52 (dt, 1H, *J* = 5, 15.5 Hz, H-9), 1.15 (s, 3H, CH_3-17), 1.11 (m, 1H, H-7), 0.91 (s, 3H, CH_3-19); ^{13}CNMR (125 MHz, $CDCl_3$, δ ppm) 198.88 (C=O-13), 170.33 (OAc-C=O), 169.95 (OAc-C=O), 160.25 (C-11), 143.51 (C-4), 133.3 (C-12), 114.59 (C-20), 77.1 (C-5), 70.59 (C-2), 48.44 (C-1), 42.78 (C-9), 40.74 (C-3), 38.58 (C-8), 38.52 (C-15),36.83 (C-17), 36.01 (C-14), 33.99 (C-7), 28.79 (C-6), 26.52 (C-10), 24.45 (C-16), 22.74 (C-19), 21.46 (OAc- CH_3), 21.39 (OAc- CH_3), 13.71 (C-18).

Spectral data of compound **6**: pale yellow film; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) 6.04 (dd, 1H, *J* = 12, 5.4 Hz, H-10), 5.54 (d, 1H, *J* = 3 Hz, H-2), 4.64 (br.s, 1H, H-5), 3.93 (d, 1H, *J* = 9.9 Hz, H-20), 3.68 (d, 1H, *J* =9.9 Hz, H-20), 3.13 (d, 1H, *J* = 20.4 Hz, H-14), 3.04 (s, 3H, $\underline{CH_3}SO_2$), 2.85 (d, 1H, *J* = 3.9 Hz, H-3), 2.75 (dd, 1H, *J* = 6.9, 20.4 Hz, H-14), 2.43 (dd, 1H, *J* = 12.6, 14.7 Hz, H-9), 2.17 (s, 3H, OAc-CH_3-10), 2.09 (s, 3H, OAc-CH_3-2), 2.08 (s, 3H, CH_3-18), 2.00 (m, 2H, H-7, H-1), 1.85 (m, 2H, 2×H-6), 1.68 (s, 3H, CH_3-16), 1.58 (dd, 1H, *J* = 5.4, 14.7 Hz, H-9), 1.24 (m, 1H, H-7), 1.16 (s, 3H, CH_3-17), 0.81 (s, 3H, CH_3-19);

Spectral data of compound **7**: colorless film; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm) 5.10 (br.s, 1H, H-20), 5.02 (dd, 1H, *J* = 11, 6 Hz, H-10), 4.98 (s, 1H, H-20), 4.28 (d, 1H, *J* = 5 Hz, H-2), 3.95 (br.s, 1H, H-5), 3.14 (d, 1H, *J* = 6 Hz, H-3), 2.65 (dd, 1H, *J* = 7, 20 Hz, H-14), 2.43 (d, 1H, *J* = 19.5 Hz, H-14), 2.31 (dd, 1H, *J* = 11.5 Hz, 14.5 Hz, H-9), 2.11 (d., 1H, *J* = 6 Hz, H-1), 2.01 (s, 3H, CH_3-18), 2.01-1.93 (m, 1H, H-7), 1.67 (m+s, 4H, H-9, CH_3-16), 1.55 (m, 2H, 2×H-6), 1.14 (s, 3H, CH_3-17), 1.04 (m, 1H, H-7), 0.95 (m, 30H, TES-$\underline{CH_3}$, CH_3-19), 0.71-0.5 (m, 18H, TES-$\underline{CH_2}$);

Spectral data of compound **8**: colorless film; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) 5.43 (br.s, 1H, H-20), 5.02 (s, 1H, H-20), 4.96 (dd, 1H, *J* = 10.8, 6 Hz, H-10), 4.23 (m, 1H, H-13), 4.17 (d, 1H, *J* = 4.8 Hz, H-2), 4.08 (br.s, 1H, H-5), 2.95 (d, 1H, *J* = 4.8 Hz, H-3), 2.73 (d, 1H, *J* = 12.6 Hz, OH-13), 2.62 (dt, 1H, *J* = 9.6, 16.8 Hz, H-14), 2.17 (dd, 1H, *J* = 11.7, 14.7 Hz, H-9), 2.01 (s, 3H, CH_3-18), 1.98 (m, 1H, H-7), 1.73 (m, 3H, 2×H-6, H-1), 1.56 (m+s, 4H, H-14, CH_3-16), 1.43 (dd, 1H, *J* = 5.7, 14.7 Hz, H-9), 1.05 (m, 1H, H-7), 0.98 (s, 3H, CH_3-17), 0.93 (m, 27H, TES-$\underline{CH_3}$), 0.82 (s, 3H, CH_3-19), 0.71-0.5 (m, 18H, TES-$\underline{CH_2}$);

NOE analysis of compound **8** at C-13:



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