Chemistry of Natural Compounds, Vol. 48, No. 4, September, 2012 [Russian original No. 4, July–August, 2012]

A FACILE SEMISYNTHESIS OF 2′,7-BISACETYLTAXOL FROM 10-DAB[a]

Min Gu,[1,2] Yang-Ming Zhang,[2] Wei Luo[2], Wei Lu,[1*] and Fa-Jun Nan[2*]

UDC 547.913.6

Paclitaxel (taxol)(**1**) [1], originally isolated from the Pacific yew tree in the early 1960s, holds great promise as a treatment for various forms of cancer, including ovarian cancer, breast cancer, and other cancers [2]. Paclitaxel is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions [3].

In the meantime, a large number of taxol derivatives and taxanes were isolated from natural sources or partially synthesized from a simple and more easily accessible taxol congener [4]. 2′,7-Bisacetyltaxol (**2**), an acetylated taxol derivative, was first isolated from the acetylated "post-taxol" fraction of *Taxus brevifolia* Nutt. [5]; later it was prepared by acetylation of taxol in the presence of acetic anhydride/dicyclohexylcarbodiimide/4-dimethylaminopyridine in dichloromethane [6b].

Biological activity evaluation showed that this compound does not promote microtubule assembly nor inhibit [^{3}H] taxol binding to microtubule protein competitively *in vitro*; it showed moderate activity in cytotoxicity assay toward the macrophage-like cell line J774.2 *in vivo*, approximately 10-fold less active than taxol in the same assay [6]. These results suggested that this compound might be converted intracellularly to either taxol, 7-acetyltaxol, or other unknown active taxol metabolites. In addition, no further activity study regarding this compound is available so far, and there is a need to explore an easier method for large-scale preparation of taxol acetate for further biological research. In the present paper, we describe a facile preparation of 2′,7-bisacetyltaxol from 10-deacetylbaccatin III (**10-DAB**), which is readily available in relatively high yield from the needle of the European yew *T. baccata*. Employing the present method, we obtained grams of sample in high overall yield. The starting material, acid **6**, can be the easily prepared by literature method [7].

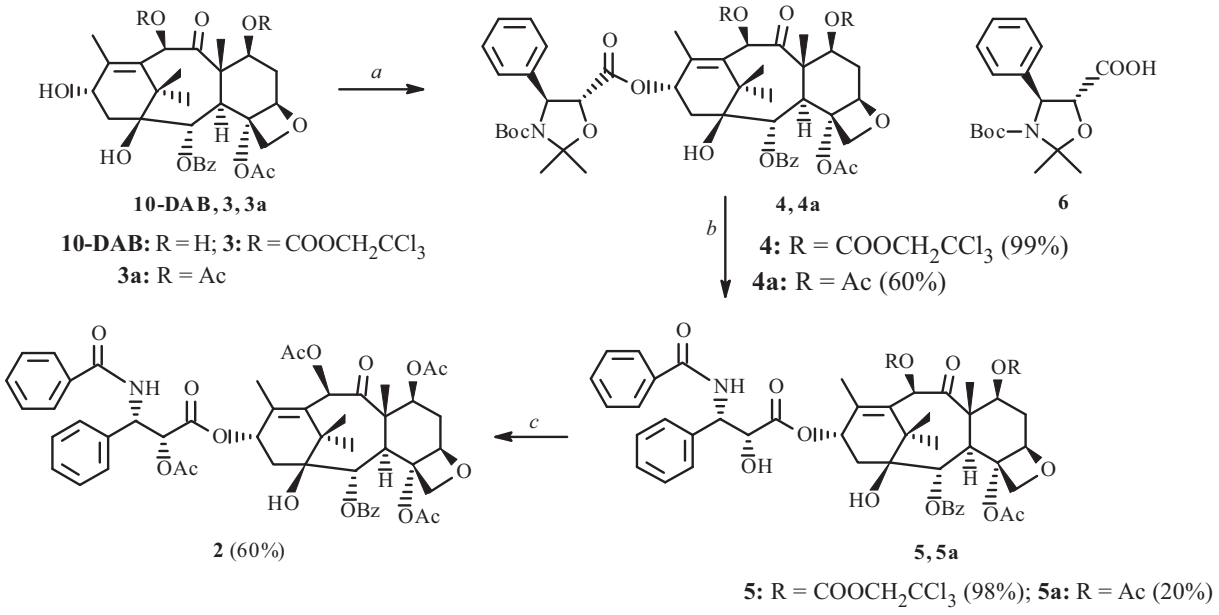
In a pervious attempt, we employed the acetyl group to protect the hydroxyl groups at the 7- and 10-positions, which is required in title compound **2** (Scheme 1). Although the esterification reaction of acid **6** with **3a** afforded **4a** in modest yield, subsequent deprotection by formic acid gave a very complex mixture due to the partial deacetylation under these conditions. After benzoylation in ethyl acetate–H_2O, compound **5a** was only obtained in 20% yield from **4a**. However, when the procedure reported in [7], was used, the 7- and 10-position hydroxyl groups were protected by 2,2,2-trichloroethoxycarbonyl (Troc). Esterification of acid **6** with **3** afforded the corresponding ester **4** in almost quantitative yield. Deprotection in formic acid at room temperature and removal of the formic acid under reduced pressure, followed by benzoylation without further treatment, yielded compound **5** in 98% overall yield. Significant improvement was observed compared to the separate procedure reported in [7]. The Troc group was then removed, followed by acetylation in Ac_2O–pyridine in the presence of DMAP. The title compound **2** was obtained in 60% overall yield from **5**. All the spectral data of compound **2** from the present experiment are in agreement with those reported previously.

---

[a]Materials presented at the 9th International Symposium on the Chemistry of Natural Compounds (SCNC, People′s Republic of China, Urumqi, Oct. 16–19, 2011).

1) Shanghai Engineering Research Center of Molecular Therapetics and New Drug Development, East China Normal University, 3663 North Zhong Shan Road, 200062, Shanghai, P. R. China, fax: +86 21 508 009 54, e-mail: wlu@chem.ecnu.edu.cn; 2) The National Center for Drug Screening, State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 189 Guo Shou Jing Road, 201203, Shanghai, P. R. China, e-mail: fjnan@mail.shcnc.ac.cn. Published in *Khimiya Prirodnykh Soedinenii*, No. 4, July–August, 2012, pp. 625–626. Original article submitted March 5, 2011.

 0009-3130/12/4804-0702



a. **6**, DCC, DMAP, toluene; *b*. *i*) HCOOH, *ii*) benzoyl chloride, $NaHCO_3$, EtOAc/H_2O; *c*. *i*) Zn, AcOH/MeOH, *ii*) Ac_2O/Py

Scheme 1. Semisynthesis of 2′,7-bisacetyltaxol from **10-DAB**.

2′,7-Bisacetyltaxol (2), mp 207–208°C, $[\alpha]_D^{20}$–49.2° (*c* 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.16 (3H, s), 1.21 (3H, s), 1.81 (3H, s), 1.87 (3H, s), 2.03 (3H, s), 2.16 (6H, 2s), 2.37 (1H, m), 2.44 (3H, s), 2.62 (1H, m), 3.95 (1H, d, J = 7.2), 4.26 (2H, dd, J = 8.4, 8.1), 4.96 (1H, d, J = 8.1), 5.58 (2H, m), 5.69 (1H, d, J = 6.9), 5.94 (1H, d, J = 3.3), 5.97 (1H, d, J = 3.0), 6.24 (2H, m), 6.92 (1H, d, J = 9.0), 7.44 (7H, m), 7.51 (3H, t), 7.61 (1H, t) 7.75 (2H, d, J = 7.2), 8.12 (2H, d, J = 6.9). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 10.07, 14.32, 14.64, 20.68, 20.92, 21.30, 21.46, 22.80, 22.86, 26.67, 31.79, 33.54, 35.64, 43.48, 47.15, 53.03, 56.22, 71.58, 71.98, 73.98, 74.78, 75.47, 76.57, 77.43, 78.90, 81.12, 84.23, 126.77, 127.29, 128.68, 128.97, 129.28, 129.36, 130.41, 132.24, 132.71, 133.93, 137.17, 141.35, 167.15, 167.36, 168.41, 169.08, 169.82, 170.01, 170.54, 202.28.

The above reaction sequence is suitable for large-scale synthesis. Following the present route, we can efficiently prepare multigrams of the target taxol acetate **2** in high overall yield.

REFERENCES

1. M. C. Wani, H. L. Taylor, M. E. Wall, P. Coggon, and A. T. McPhail, *J. Am. Chem. Soc*., **93**, 2325 (1971).
2. E. K. Rowinsky, L. A. Cazenave, and R. C. Donehower, *J. Natl. Cancer Inst*., **82**, 1247 (1990).
3. a) P. B. Schiff, J. Fant, and S. B. Horwitz, *Nature*, **277**, 665 (1979); b) J. J. Manfredi and S. B. Horwitz, *Pharmacol. Ther.,* **25**, 83 (1984).
4. a) D. G. I. Kingston, *History and Chemistry, in Paclitaxel in Cancer Treatment*, W. P. Mcguire and E. K. Rowinski, (eds.), Marcel Dekker, New York, Basel, Hong Kong, **8,** 1995, pp. 1–33; b) Y. F. Wang, Q. W. Shi, M. Dong, H. Kiyota, Y. C. Gu, and B. Cong, *Chem. Rev*., **111**, 7652 (2011).
5. D. G. I. Kingston, D. R. Hawkins, and L. J. Ovington, *J. Nat. Prod.*, **45**, 466 (1982).
6. a) J. Parness, D. G. I. Kingston, R. G. Powell, C. Harracksingh, and S. B. Horwitz, *Biochem. Biophys. Res. Commun.*, **105**, 1082 (1982); b) W. Mellado, N. F. Magri, D. G. I. Kingston, R. Garcia-Arenas, G. A. Orr, and S. B. Horwitz, *Biochem. Biophys. Res. Commun.*, **124**, 329 (1984).
7. A. Commercon, D. Bezard, F. Bernard, and J. D. Bourzat, *Tetrahedron Lett.,* **33**, 5185 (1992).