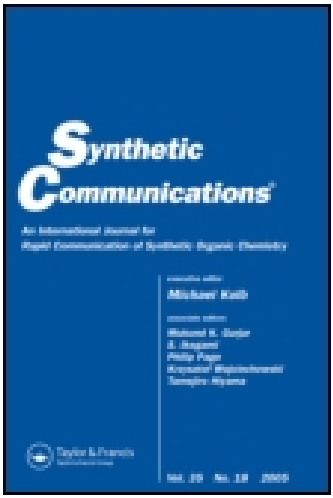


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Reinvestigation to the C-7 Epimerization of Paclitaxel and Related Taxoids Under Basic Conditions

Wei-Shuo Fang [a] , Qi-Cheng Fang [a] & Xiao-Tian Liang [a]

[a] Institute of Materia Medica, Chinese Academy of Medical Sciences & Peking Union Medical College , Beijing, 100050, P. R. China
Published online: 22 Aug 2006.

To cite this article: Wei-Shuo Fang , Qi-Cheng Fang & Xiao-Tian Liang (1997) Reinvestigation to the C-7 Epimerization of Paclitaxel and Related Taxoids Under Basic Conditions, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 27:13, 2305-2310, DOI: 10.1080/00397919708003386

To link to this article: http://dx.doi.org/10.1080/00397919708003386

SYNTHETIC COMMUNICATIONS, 27(13), 2305-2310 (1997)

REINVESTIGATION TO THE C-7 EPIMERIZATION OF PACLITAXEL AND RELATED TAXOIDS UNDER BASIC CONDITIONS

Wei-Shuo FANG, Qi-Cheng FANG* and Xiao-Tian LIANG

Institute of Materia Medica, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100050, P. R. China

Abstract: Base-promoted C-7 epimerizations of paclitaxel, 10-deacetylbaccatin III were investigated. It has been found that 13α-OH may play an important role in the equilibrium of C-7 epimers of paclitaxel and related taxoids.

Paclitaxel(taxol) has become a star molecule for its complexity of chemical structure, excellent antitumor activity and unique action on microtubules[1]. Many efforts on structural modification of pacletaxel, 10-deacetyl baccatin III and related taxoids had been made, such as deoxygenation[2], cleavage[3], A-[4], B-[5] and C-ring[6] contraction and amination.[7] In these reactions, especially under basic or base-catalyzed conditions, C-7 epimerization was frequently observed.

* To whom correspondence should be addressed

The hydroxyl group at C-7 easily undergoes epimerization through retro-aldol reaction[1a,8], leading to the formation of C-7 epimer mixture. Kingston et al[9] reported that paclitaxel(**3A**) can be converted to 7-epi-paclitaxel(**3B**) after treatment with stoichiometric amounts of sodium hydride in tetrahydrofuran in moderate yield. Khuong-Huu et al[3b] treated 13-acetyl-10-deacetylbaccatin III(**5**) with DBU in toluene, yielding its 7-epimer in 80% yield. And DBU/toulene also converted 10-deacetylpaclitaxel(**1A**) into 7-epi-10-deacetylpaclitaxel(**1B**). It seems rational that 7a-epimers predominate in the mixture of epimers, since 7α -OH series paclitaxel analogs can be stabilized by the intramolecular hydrogen bond between 7α -OH and 4-OAc. But reverse results were also observed. Appendino et al[10] obtained 7β-OH-10-epi-10-deacetylbaccatin III(**6**) after treatment of 10-deacetyl-10-oxobaccatin III(**7A**) or 10-deacetyl-10-oxobaccatin V(**7B**) with sodium borohydride. They postulated that the hydrogen bond between 10α-OH and 4-OAc may control the conformation of C8-C9 enolate to the addition of C-6 aldehyde. Steric factors determine the predomination of 7β-epimer. Holton et al[2a] also reported Sm^{3+} may influence the conversion of 7α- to 7β-epimer. As a whole, C-7 epimerization was not thoroughly studied to date.

During our tests on selective hydrolysis of 7-epi-10-deacetylpaclitaxel(**1B**) which is abundant in *Taxus yunnanensis*, various kinds of bases and alkaline salts, such as sodium methoxide, sodium hydroxide, potassium carbonate, sodium bicarbonate and hydrazine, and nucleophilic reagents such as potassium cyanide were used. It was found that the mixture of hydrolysed products, at room temprature or in ice bath, usually consist of 10-deacetylbaccatin III(**2A**) as major product and 10-deacetylbaccatin V(**2B**) as minor product if the reaction time was long enough. After careful monitoring of the hydrolysis of **1B** with potassium carbonate in methanol, we noticed that the starting material was hydrolysed to **2B** quickly at first, and then **2B** epimerized into **2A** gradually, forming a mixture consisted of approximately 7β:7α (2.2:1) epimers finally.

This phenomenon drew our attention to a thorough study on the interconversion of 7α and 7β epimers. **2A** and **2B** were treated with

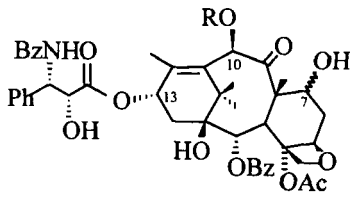
stoichiometric or excess sodium hydride and DBU, which has been used in the preparation of 7α-epimers from 7β-epimers of paclitaxel and its analogs. In the case of NaH, some more polar products were formed before 7α/7β mixtures reached equilibrium. And in the case of DBU, the final mixture contained about 2.8:1 of 7β:7α epimers. Obviously, base-promoted epimerization of **2A** and **2B** favors 7β epimers.

Considering DBU has little tendency to give rise to hydrolysis of carboxylic esters, we chose this reagent to explore the interconversion of 7α and 7β epimers of paclitaxel and related taxoids. Paclitaxel(**3A**) and 7-epi-paclitaxel(**3B**) formed a mixture of about 2:1 (7α:7β) epimers. 10-Deacetylpaclitaxel(**1A**) and 7-epi-10-deacetylpaclitaxel(**1B**) formed 6:1 to 7:1 (7α:7β) epimers at equilibrium point. In the baccatin III(**4A**) case, a mixture of nearly 1:1 of 7α:7β epimers was obtained.

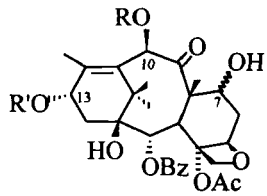
Our experimental results and those results from the literature[3b, 8-10] can be rationalized as the influence of intramolecular hydrogen bonding between 13α-OH an 4-OAc which has been well known from its crystal structure[12] and its reactivities against other secondary hydroxyl in the molecule[1b, 13]. It is noteworthy that in those compounds with C-13α hydroxyl group(**2A-B, 4A-B**), stabilization of 7α-OH series were weakened by the formation of the hydrogen bonding between 13α–OH and 4-OAc. Furthermore, the hydrogen bond between 13α-OH and 4-OAc may also contribute to the conformation of the intermediate(**8**) which favors the formation of 7β-OH series products.

We have calculated the energy of 7β(**1A**, **3A**) and 7α(**1B**, **3B**) hydroxyl compound. In line with our hypothesis, the results showed that the energy of 7α-OH-10-deacetylbaccatin III is higher than that of 10-deacetylbaccatin III, due to the loss of stabilization attributed to the intramolecular hydrogen bonding between 7α-OH and 4-OAc.

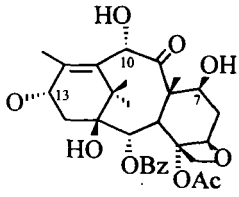
In conclusion, the 13α-OH may play an important role in the C-7 epimerization of paclitaxel and its analogs. Our finding can also be applied to the



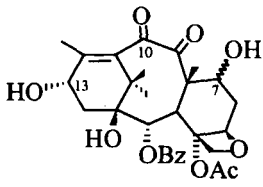
1A R=H, 7β-OH
1B R=H, 7α-OH
3A R=Ac, 7β-OH
3B R=Ac, 7α-OH



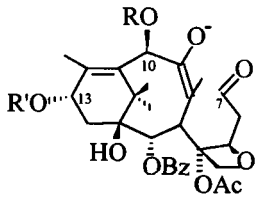
2A R=H, R'=H, 7β-OH
2B R=H, R'=H, 7α-OH
4A R=Ac, R'=Ac, 7β-OH
4B R=Ac, R'=Ac, 7α-OH
5 R=H, R'=Ac, 7β-OH



6



7A 7β-OH
7B 7α-OH



8

preparation of 10-deacetylbaccatin III from 7-epi paclitaxel analogs which are abundant in natural resources.

Experimental

General Procedure for the treatment of taxoids with DBU.-- To a solution of taxoid(5μmol) dissolving in 0.2ml of xylene, 25μl of DBU was added. The solution was heated at a 80°C oil bath with stirring. The reaction was monitored with Si gel plate eached 5 min. When it reached equilibrium point(usually 0.5 to 1 hr), reaction mixture was checked with HPLC. The reaction was continued for another 0.5 h to ensure it equilibrated, and final mixture was also examined with HPLC.

Calculation of the energy of taxoids.-- The calculation of energy was performed in TRIPOS field, without consideration of charge. The minimization was continued

until the delta energy reached 0.001 kcal/mol. When minimization started from 10-deacetyl baccatin III, the energy of 7-epi-10-deacetylbaccatin III(72.341 kcal/mol) is lower than that of its 7β-epimer(77.448 kcal/mol) due to the predominant formation of intramolecular hydrogen bond between 7α-OH and 4-OAc. When the minimization started from 7-deoxy-10-deacetylbaccatin III, 13α-OH formed hydrogen bond with 4-OAc. The energy of 7-epi-10-deacetylbaccatin III was enhanced to 63.365 kcal/mol and thus higher than that of 10-deacetylbaccatin III(62.795 kcal/mol). When 13α-OH was acylated, the energies of 7α-epimers, such as 7-epi-10-deacetylpaclitaxel, were lower than those of 7β-epimers as expected.

Acknowledgement

The authors thank gratefully Dr. Nan Wu for the help during our calculation of the energy of taxoids.

References

1.For recent review see

Kingston, D.G.I.; Moliner, A.A. and Rimoldi, J.M. *Prog. Chem. Org Nat. Prod.*, Spriger-Verlag, New York, **1993**, *61*, pp.1-206;

2. (a) Holton, R.A.; Somoza, C. and Chai, K.-B. *Tetrahedron Lett.*, **1994**, *35*, 1665;

(b) Chen, S.-H.; Wei, J.-M. and Farina, V. *Tetrahedron Lett.*, **1993**, *34*, 3205;

(c) Chen, S.-H.; Wei, J.-M.; Vyas, D.M.; Doyle, T.W. and Farina, V. *Tetrahedron Lett.*, **1993**, *34*, 6845;

3. (a) Chordia, M.D.; Gharpure, M.M. and Kingston, D.G.I. *Tetrahedron.*, **1995**, *51*, 12963;

(b) Py, S; Pan, J-W. and Khuong-Huu, F. *Tetrahedron.*, **1994**, *50*, 6881;

4. Samaranayake, G.; Magri, N.F.; Jitrangsri, C. and Kingston, D.G.I. *J. Org. Chem.*, **1991**, *56*, 5114;

5. Klein, L.L.; Maring, C.J.; Li, L.; Yeung, C.M.; Thomas, S.A.; Grampovnik, D.J.; Plattner, J.J. and Henry, R.F. *J. Org. Chem.*, **1994**, *59*, 2370;

6. Liang, X.; Kinsgston, D.G.I.; Long, B.H.; Fairchild, C.A. and Johnston, K.A. *Tetrahedron Lett.*, **1995**, *36*, 7795;

7. Chen, S-H.; Farina, V.; Vyas, R.M.; Doyle, T.W.; Long, B.H. and Fairchild, C. *J. Org. Chem.*, **1996**, *61*, 2065;

8. McLaughlin, J.L.; Miller, R.W.; Powell, R.G. and Smith Jr., C.R. *J. Nat. Prod.*, **1981**, *44*, 312;

9. Chaudhary, A.G.; Rimoldi, J.M. and Kingston, D.G.I. *J. Org. Chem.*, **1993**, *58*, 3798;

10. Gao, Q. and Parker, W.L. *Tetrahedron.*, **1996**, *52*, 2291;

11. Appendino, G.; Jakupovic, J; Cravotto, G.; Enriu, R; Varese, M. and Bomvardelli, E. *Tetrahedron Lett.*, **1995**, *36*, 3233;

12. Wani, M.C.; Taylor, H.L.; Wall, M.E.; Coggon, P. and McPhail, A.T. *J. Am. Chem. Soc.*, **1971**, *93*, 2325;

13. Chen, S.-H. *Tetrahedron Lett.*, **1996**, *37*, 3935;

(Received in the UK 9th December 1996)