Pergamon

Tetrahedron Letters, Vol. 38, No. 18, pp. 3223-3226, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00583-2

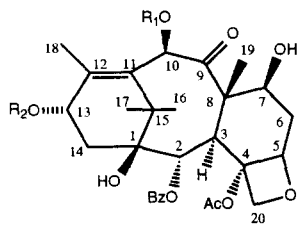
An Angular Hydroxylation Route to Taxanes: Facile Access to the Bridged AB Ring System of Taxol‡

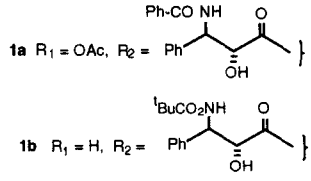
Brahim Kerkar[a], Duc Do Khac*[a], Marcel Fétizon*[a], Frédéric Guir[b].

[a] Institut de Chimie des Substances Naturelles, Centre National de la Recherche Scientifique, 91198 Gif-sur-Yvette, France.
[b] Centre d'Etudes du Bouchet, 91710 Vert-Le-Petit, France.

Abstract : The 5-mesyloxy-12-alcohol ***11b****, obtained in eight steps from* ***5a*** *, via angular hydroxylation is transformed by Grob fragmentation into the highly functionalized taxane precursor* ***12****.*

Taxol® **1a** and Taxotere® **1b** are used in the treatment of several human cancers.[1] Since taxol was first isolated in small quantity from the bark of yew trees[1], a great deal of work has been undertaken aiming at either a total or a partial synthesis of the drug.[2] Although three total syntheses of taxol have been successful [3], the need for shorter and more flexible routes remains a challenge.





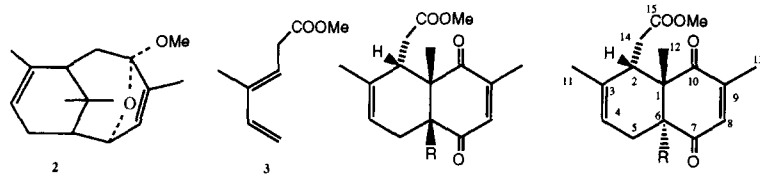
Some years ago, we carried out a simple total synthesis of the bicyclic precursor **2** from readily accessible and cheap substances.[4] The key step of the synthesis was the cycloaddition of diene **3** to 2,5-dimethylbenzoquinone (obtained by Jones oxidation of 2,5-dimethylphenol).

---

‡*This paper is dedicated to Professor Truong Cong Quyen. Faculty of pharmacy Ha-Noi University of Viet-Nam, on the occasion of his 89th birthday and for his studies of vietnamese medicinal plants.*

This reaction turns out to be regio-and stereo-selective, and leads to **4a** in high yield. However, when a large scale preparation of **4a** was attempted, a very fast epimerisation of the expected compound took place (probably due to some acidic impurities remaining in the quinone) and led to **5a**, so that we were left with more than 500 g of apparently useless **5a** (mp 112°C $C_{16}H_{20}O_4$, Xrays).[4]

We have now found that the latter compound can be specifically α-hydroxylated at C_6 by treatment with Barton's reagent (benzeneseleninic anhydride).[5]



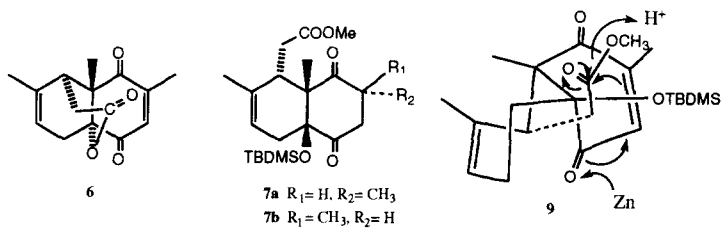
2 3

4a R = H
4b R = OH
4c R = OTBDMS

5a R= H
5b R= OH

This reaction was successfully carried out, although the yield in the desired product remains modest. The crude oxidation mixture consists of **4b**, its isomer **5b** and the corresponding lactone **6**. Since their separation was difficult, this mixture was treated in CH_2Cl_2 with a trace of TsOH. Under these conditions, **5b** gave the lactone **6** (53% yield, m.p: 141-142°C, $C_{15}H_{16}O_4$), easily separated from **4b** (27% yield, m.p. 91-92°C, $C_{16}H_{20}O_5$). Although the hydroxyl group in **4b** is severely hindered, it could easily be protected as the t-butyldimethylsilyl ether **4c** (TBDMS-Triflate, 2,6-lutidine, 0°C, then room temperature, quantitative yield, m.p. 109-110°C, $C_{22}H_{34}O_5Si$).

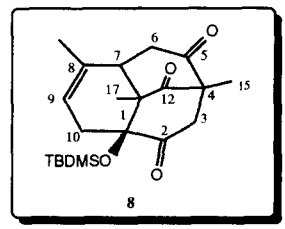
Ultrasonication of **4c** (Zn dust, CH_3OH, AcOH-H_2O, 20 mn) affords in high yield a mixture of the expected dihydro-compounds **7a** and **7b** (23%) and, rather surprisingly, the triketone **8** (67%, m.p. 81-82°C, $C_{31}H_{32}O_4Si$, ICMS $[M+H]^+$ 377). The NMR spectra (^1H and ^{13}C) suggested that the largely preferred conformation of **4c** is **9**, so that reduction through intramolecular Claisen cyclisation of **4c** into **8** is quite reasonable.



6

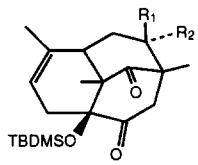
7a R_1= H, R_2= CH_3
7b R_1 = CH_3, R_2= H

9

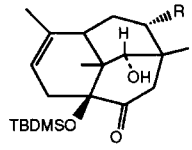


8

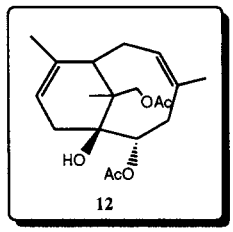
The three keto groups of **8** have different reactivities. Luche reduction ($NaBH_4$-$CeCl_3$,$7H_2O$-MeOH) at 0°C was regio- and highly stereo-selective and gave **10a** (90%, m.p. 92-93°C, $C_{21}H_{34}O_4Si$), in addition to a small amount of the β isomer **10b** (10%, m.p. 178-180°C, $C_{21}H_{34}O_4Si$).[6] A further reduction ($NaBH_4$/MeOH, rt) of **10a** gave quantitatively a single dihydroxyketone **11a** (m.p: 103-104°C, $C_{21}H_{36}O_4Si$), which affords a single mesylate **11b** (mesylic anhydride, pyridine 0°C then rt; m.p. 146-147°C, $C_{22}H_{38}O_6SiS$).



10a . R_1 = H. R_2 = OH
10b . R_1 = OH. R_2 = H



11a , R= OH
11b , R = OMs



12

The Grob fragmentation was accomplished by treatment of **11b** with LAH/DME (2 molar equivalents, 85°C, 2h), followed by acetylation, affording the bridged AB taxane precursor **12** (m.p. 99-100°C, $C_{19}H_{28}O_5$) in 60% yield. Further work is in progress, in view of introducing ring C.

Acknowledgements: We are grateful to the CNRS for a financial help, to Prof. P. Potier for a generous support, as well as for his permanent encouragement, and to the Ligue Nationale contre le Cancer for a scholarship to (B.K).

References:

1-(a)Taxol and taxotere: Discovery, chemistry, and structure-activity relationships; Guénard, D.; Guérrite-Voegelin, F.; Potier, P. *Acc. Chem. Res.* **1993**, *26*, 160-167.

(b)Taxane Anticancer Agents: Basic science and current status; Georg, G.; Chen, T.; Ojima, I.; Vyas, D.; Eds. *ACS Symposium Series 583*; *American Chemical Society*; Washington, DC, **1995**.

2-(c)Taxol is the registred trademark for the molecule with generic name paclitaxel. For a recent review of synthetic studies from over 35 groups, see Wender, P.A.; Natchus, M.G; Shuler, A.J. in Taxol Science and Applications; Suffness. M.; Ed. *CRC Press* New York, **1995**; pp 123-187.

(b)Kingston, D. G. I.; Molinero, A. A.; Rimoldo, J. M. The Taxane Diterpenoids *in* Progress in the Chemistry of Natural Products, vol 61, **1993**, 1-206, *Springer-Verlag*, New-York.

3-(a)Holton, R. A.; Somoza, C.; Kim, H. B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Slimdo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zang, P.; Murthi, K. K.; Gentile, L. N.; Liu,J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1597-1598, ibid 1598-1600.

(b)Nicolaou, K. C.; Yang, Z.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Clairborne, C. F.; Renaud, J. Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, 367-630.

(c)Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Coburn, C. A.; Di Grandi, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2843-2859.

4- Benchikh le Hocine, M.; Do Khac, D.; Fétizon, M.; Guir, F.; Prangé, T. *Tetrahedron Lett.* **1992**, *33*, 1443-1446.

5-(a)Barton, D. H. R.; Hui, A. H. F.; Lester, D. J.; Ley, S. V. *Tetrahedron Lett.* **1979**, 3331-3334.

(b)Yamakawa, K.; Satoh, T.; Ohba, N.; Sagaguchi, R.; Takita, S.; Tamura, N. *Tetrahedron Lett.* **1981**, *37*, 473-479.

6-Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.*, **1981**, *103*, 5454-5459.

(*Received in France* 8 *February* 1997; *accepted* 21 *March* 1997)