Pergamon

Tetrahedron Letters, Vol. 37, No. 51, pp. 9189-9192, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)02152-1

Chemistry of Taxoids : One-step Functionalization of the Positions 1, 2, 9 and 10 from the Selectively Protected 5-O-Cinnamoyltaxicine I

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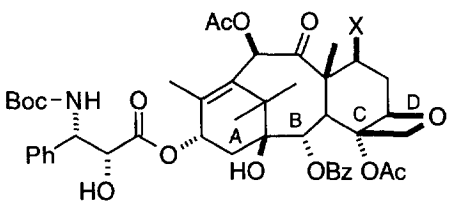
Abstract : A simple one-step oxidative functionalization of the positions 1, 2, 9 and 10 of 5-O-cinnamoyltaxicine I is described. The benzylidene and ethylidene acetals were used as protective groups on the diols 1,2 and 9,10 respectively ; their simultaneous direct conversion into 1-hydroxy-2-benzoyloxy and 9-keto-10-acetoxy derivative was achieved by CrO_3/AcOH or the Jones reagent. Copyright © 1996 Published by Elsevier Science Ltd

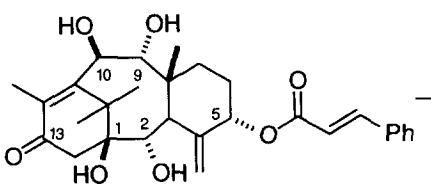
In our efforts to discover novel active analogues of docetaxel **1** and 7-deoxy-docetaxel **2** by semisynthesis using the readily available taxoid skeleton, we became interested in the access to the **B** ring of docetaxel **1.**



1 : X = OH
2 : X = H

The 5-O-cinnamoyltaxicine I **3** was prepared according to the reported procedure [1-3] by deamination and deacetylation of the major alkaloids isolated from the needles of the European yew tree.

Alkaloids isolated from the European yew tree (5-7 g/Kg)



Analogues of **1**

3

The choice of appropriate protective groups is a major problem for the synthesis of these polysubstituted taxoid derivatives. Furthermore, the use of specific protective groups is limited by the tolerance of the already highly functionalized and substituted intermediate taxoids to various deprotecting reagents. In our particular

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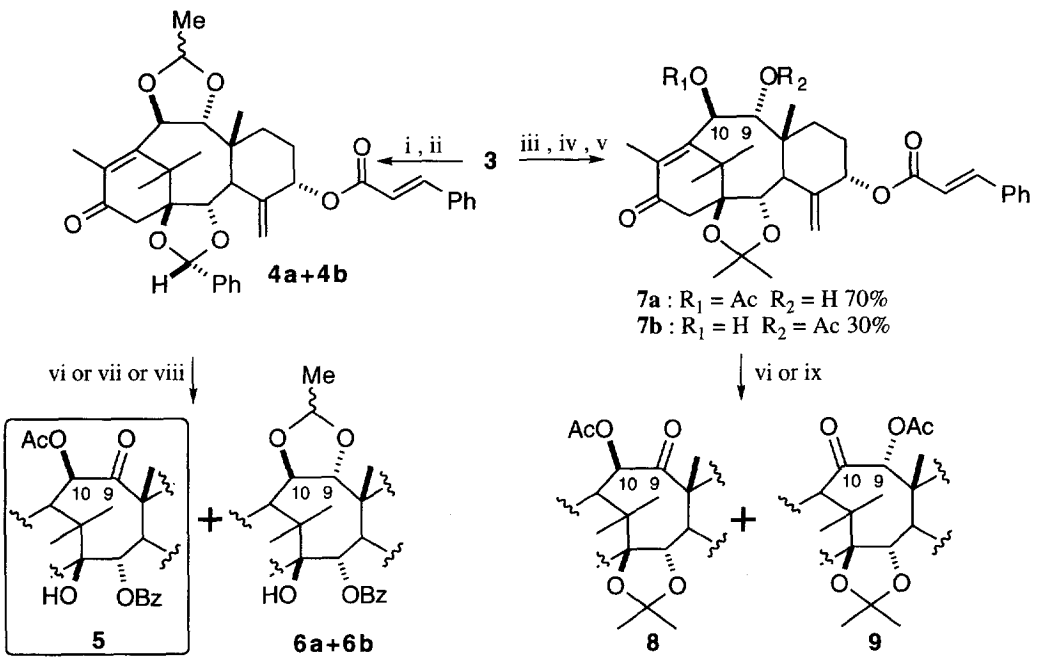
case, while the deprotection into the free hydroxyls is successful, their selective substitution and conversion to the desired functions remain problematic. The currently known taxoid chemistry shows that the problem with chemoselective approaches is the difficulty to prevent rearrangements of the diterpene skeleton. An alternative which avoids such complications involves masked functions as protective groups with convenient substituents and their direct transformation into the desired product in one step.

Nicolaou introduced the 1,2-carbonate and described its regioselective opening into the 1-hydroxy-2-benzoate with an excess of phenyllithium.[4, 5]

Several cyclic acetal protected diols have been used for this purpose [6-10] : thus, benzylidene or ethylidene acetal protected diols could be converted into the corresponding hydroxy-esters and keto-esters *via* an oxidation in acidic conditions.



(i) : 2 equiv. of $PhCH(OCH_3)_2$; (ii) : excess $MeCH(OCH_3)_2$; (iii) : acetone, H_2SO_4 ;
(iv) : 60% AcOH in water/MeOH : 7/3, 4 days ; (v) : 2 equiv. Ac_2O, DMAP, Pyridine ;
(vi) : Jones reagent ; (vii) : CrO_3/AcOH ; (vii) : $RuCl_3$/t-BuOOH ; (ix) : TPAP/NMO

The mixture of epimers **4a+4b** [11] was obtained from **3** over two steps[12] involving an exchange (benzylidene → ethylidene) which took place exclusively and quantitatively on positions 9 and 10. Treatment of **4a+4b** with CrO_3 in glacial acetic acid afforded the compound **5** with the desired functionalized **B** ring of docetaxel in 24% yield.[13] The partially oxidized 1-hydroxy-2-benzoate was also isolated (8% yield) as a mixture of two epimers **6a+6b**.

The regioselective conversion of the highly oxidant-labile 1,2-benzylidene acetal into 1-hydroxy -2-benzoate could be achieved using Jones reagent, $CuCl_2$/tBuOOH or CrO_3/AcOH. The oxidation of the

ethylidene acetal was more difficult. Its cleavage by CrO_3/AcOH leads to two regiomeric ketoesters. Only the regiomer **5** could be isolated, with the by-products **6a+6b**. The other regiomer is probably over-oxidized to polar unstable by-products. To prevent this decomposition, milder oxidizing conditions were used. Treatment of **4** with $RuCl_3$/ t-BuOOH leads only to 51% of the intermediates **6a+6b**. By using Jones oxidation, only **5** was isolated but the yield is lowered to 19%. In all attempts, the regiomeric 9-acetoxy-10-ketone has never been observed as a by-product. Mechanistically, the oxidative opening of acetals to ketoesters is believed to proceed via hydroxyesters.

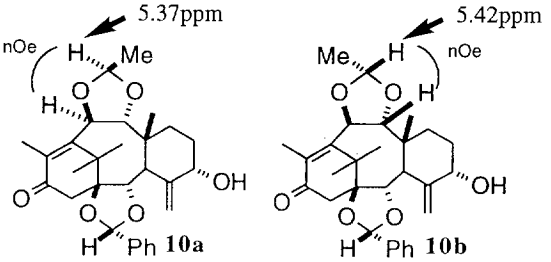
When the 9- or 10-monoacetylated regiomers **7a+7b** : 70/30 (easily obtained from tetrol **3**) have been oxidized under mild conditions, by TPAP/NMO, both regiomers **8** (22%) and **9**(8%) were isolated ; with Jones reagent, only **8** has been isolated (60% yield). The presence of an isopropylidene acetal known to be more stable than the benzylidene one in position 1 and 2, provides favourable conditions.

In summary the present procedure involving simultaneous oxidative cleavage of cyclic acetals to hydroxy- and keto-esters provides a relatively easy access to the 1, 2, 9, and 10 substituted **B** ring of the active taxoids.

References and notes

1. Ettouati, L.; Ahond, A.; Poupat , C.; Potier, P. *Tetrahedron*, **1991**, *47*, 9823-9838
2. Ettouati, L. Thèse de Doctorat en sciences de l'Université Paris-Sud, Orsay, 20 March 1991
3. Poujol, H. Thèse de Doctorat en sciences de l'Université Paris-Sud, Orsay, 13 March 1996
4. Nicolaou, K. C.; Nantermet, P. G.; Ueno, H.; Guy, R. K. *J. Chem. Soc., Chem. Commun.*, **1994**, 295-296
5. Nicolaou, K. C.; Renaud, J.; Nantermet, P. G.; Couladouros, E. A.; Guy, R. K.; Wrasidlo, W. *J. Am. Chem. Soc.*, **1995**, *117*, 2409-2420
6. Angyal, S. J.; James, K. *Aust. J. Chem.*, **1971**, *24*, 1219-1227
7. Hosokawa, T.; Imada, Y.; Murahashi, S.I. *J. Chem. Soc., Chem. Comm.*, **1983**, 1245-1246
8. Sato, K. I.; Igarashi, T.; Yanagisawa, Y.; Kawauchi, N.; Hashimoto, H.; Yoshimura, J. *Chem. Lett.*, **1988**, 1699-1702
9. Deslonchamps, P.; Moreau, C. *Can. J. Chem.*, **1975**, *49*, 2465-2467
10. Deslonchamps, P.; Moreau, C.; Frehel, D.; Chenevert, R. *Can. J. Chem.*, **1975**, *53*, 1204 -1221
11. The two epimers were separated after the hydrolysis of the cinnamate : the mixture **4a+4b** was treated with 20% NaOH in THF at reflux to afford the separable (chromatography on silica gel hept./AcOEt) epimers **10a** and **10b** (total yield 92%). [3]

    The acetal protons were individually distinguished in proton NMR spectra for each epimer by nOe studies.



12. Also obtained from one-pot dibenzylation of **1** by 2.2 equiv. of $PhCH(OMe)_2$ and the subsequent exchange of the formed benzylidene group into an ethylidene one in presence of an excess of $MeCH(OMe)_2$ in 92% yield.

13. A typical procedure for the formation of **5** and the by-products **6a+6b** is as follows :
to a stirred solution of **4a+4b** 48 mg (0.08 mmol) in 1.5 ml acetic acid, 52 mg (6 eq.) of CrO_3 are added. After stirring for 3h30 at rt, buffer phosphate (pH = 7) is added to the mixture . The aqueous layer is extracted with CH_2Cl_2. Combined organic layers are washed with brine, dried over $MgSO_4$ and concentrated. The residue is chromatographed (hep./AcOEt : 5/5). 12.3 mg (24%) of **5** and 4.3 mg (8%) of epimers **6a+6b** were isolated. **5** (2-benzoyl-5-O-cinnamoyl-9-oxo-10-acetyl taxicine I). **IR** ($CHCl_3$) : 1750, 1710, 1675. **MS** (IC): 641 (MH^+). **RMN ^{1}H** (300 MHz, $CDCl_3$) : 8.01 (dbr. 2H), 7.73 (m, 2H) ; 7.68 (d, 16 Hz,1H) ; 7.58 (m, 1H) ; 7.46 (m, 5H) ; 6.78 (s, 1H); 6.47 (d, 16 Hz, 1H) ; 5.66 (d,8 Hz, 1H) ; 5.34 (s ép., 1H) ; 5.28 (s, 1H) ; 4.58 (s, 1H) ; 4.12 (d, 8 Hz, 1H) ; 3.20 (d, 20 Hz, 1H) ; 2.74 (d, 20 Hz, 1H) ; 2.28 (s, 3H) ; 2.27 (s, 3H); 2.11 (m, 2H) ; 1.88 (m, 2H) ; 1.38 (s, 3H) ; 1.28 (s, 3H) ; 1.26 (s,3H).

14. Griffith,W. P.; Ley, S. V. *Aldrichimica Acta,* **1990**, *23,* 13-19

(*Received in France* 17 *September* 1996; *accepted* 2 *November* 1996)