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Taxoids: 11,12-Dihydro-4-deacetyldocetaxel

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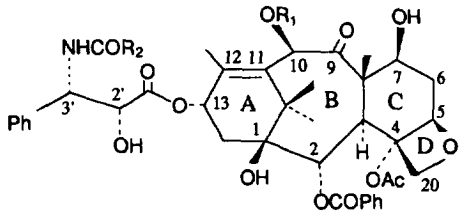
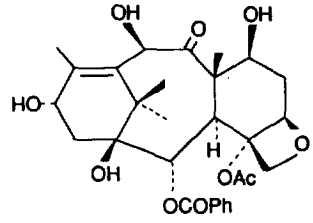
Abstract : 11,12-dihydro-4-deacetyldocetaxel was prepared from 10-deacetylbaccatin III via its reduced derivative at C11, C12. The title compound is not active on microtubules disassembly.

Taxoids are a series of new anticancer drugs[1] which inhibit cell growth by interacting with microtubules.[2] Among these substances, Taxol® (paclitaxel) **1**[3] and Taxotere® (docetaxel) **2**[4] are clinically active against ovarian, breast and lung cancers. In order to obtain new compounds with improved biological activity and to study the structure-activity relationships in this series, a number of structural modifications have been performed on paclitaxel and docetaxel. These modifications include mainly the ester groups at C-2, C-4, and C-13, the oxetane D ring as well as the oxygenated functions at C-7, C-9 and C-10[5]. On the contrary, only few analogues modified at the C-11, C-12 positions have been prepared[5e] and, to date, no information is available on the direct influence of the A-ring double bond on the antitubulin activity.



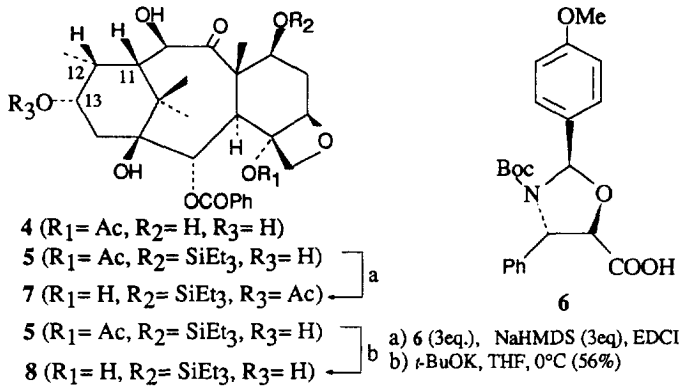
1 R_1= Ac, R_2= Ph
2 R_1= H, R_2= $O(CH_3)_3$



3

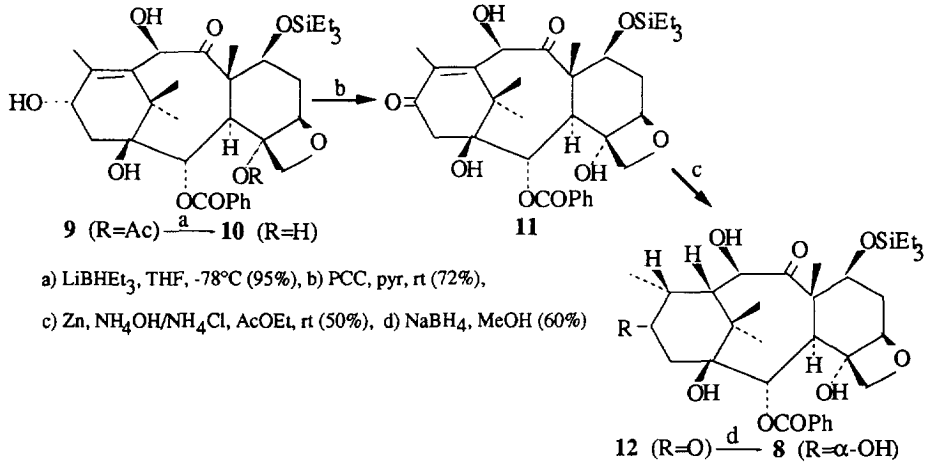
We have previously described the synthesis of 11,12-dihydro-10-deacetylbaccatin III **4** and of its 7-triethylsilyl derivative **5** from 10-deacetylbaccatin III **3**[6], a renewable precursor isolated from the leaves of the European yew tree, *Taxus baccata*.[7] Very recently, reduction of the C-11, C-12 double bond of baccatin III derivatives was also described by Appendino and coll..[8] In order to obtain the 11,12- dihydro derivative of docetaxel, compound **5** was treated with 3 equivalents of the protected acid side chain **6**[9] and a coupling agent (3 eq). Unfortunately, in our hands, no reaction occurred when we used the DCC or EDCI / DMAP procedure. On the other hand, treatment of **5** and acid side-chain **6** with NaHMDS / EDCI led to the 13-acetyl, 4-deacetyl derivative **7** (Scheme 1). The easy acyl transfer from C-4 to the hydroxyl group at C-13 can be explained by the very close proximity of these two groups as seen in the X-ray crystallography study of 11,12-dihydro-7-triethylsilyl-10-deacetylbaccatin III **5**.[10]

A solution to the C-13 acylation would be to introduce the proper acid side chain on the 4-deacetylated derivative **8** and then reacetylate the C-4 hydroxyl group. Selective approaches to the removal of the C-4 acetyl group from baccatin III derivatives have been described in the literature.[5e,11-16]



Scheme 1

Following one of these procedures,[11] the treatment of **5** with potassium *t*-butoxide afforded the desired 4-deacylated derivative **8** (Scheme 1). Compound **8** was also obtained after reduction of the 13-oxo-4-deacetylated derivative **12**. This compound was prepared from 7-TES-10-deacetylbaccatin III **9** by reduction of the acetyl group with Super-hydride[14] (compound **10**). Oxidation of **10** with PCC provided the 13-oxo derivative **11**. Finally, the double bond and the keto group were respectively reduced by zinc (compound **12**) and $NaBH_4$ to offer compound **8** (Scheme 2).

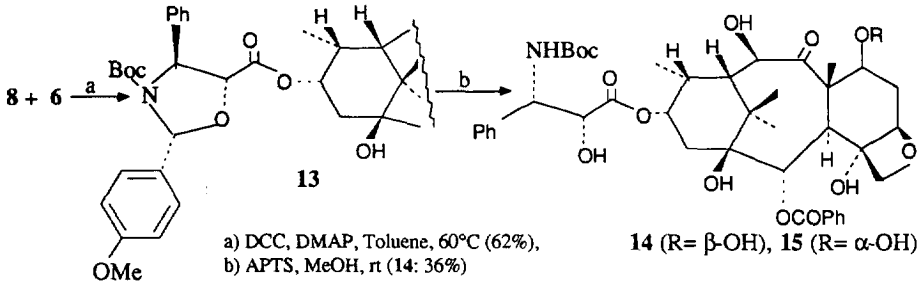


Scheme 2

The acid side chain **6**[9] was then attached to **8**, using the DCC, DMAP procedure[17] (compound **13**). Compound **13** underwent stepwise deprotection leading first to the desilylated derivative and then to 11,12-dihydro-4-deacetyldocetaxel **14**. Some epimerization at C-7 (compound **15**) also occurred under the

deprotection conditions (Scheme 3). 11,12-dihydro-4-deacetyldocetaxel **14** and its 7-epimer **15** exhibit mass, ^{1}H-NMR and ^{13}C-NMR spectra in agreement with the assigned structures.[18]

Many attempts have then been made to obtain 11,12-dihydrodocetaxel from the 4-deacetylated derivative **13**, but, to our disappointment, the hindered hydroxyl group at C-4 could not be acetylated, even under forcing conditions. For exemple, no reaction occurred when a solution of compound **13** in pyridine was treated with Ac_2O (20 eq), DMAP (20 eq) at 70°C. On the other hand, treatment with acetyl chloride under highly basic conditions (LiHMDS or NaHMDS) in THF led to the cleavage of the side-chain at C-13.



Scheme 3

Analogues **14** and **15** were evaluated *in vitro* on the disassembly process of microtubules into tubulin.[19] 11,12-Dihydro-4-deacetyldocetaxel **14** and its 7-epimer **15** are inactive.[20] In comparison, in the microtubule disassembly assay, 4-deacetyldocetaxel[21] possesses an IC_{50} of 4. 10^{-5} M. These results show that the A ring double bond is essential to the interaction of taxoids with microtubules.

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18. Spectroscopic data of the title compound **14** and its 7-epimer **15**:

14: IR ($CHCl_3$) 3495, 1718, 1706 cm^{-1}; FABMS m/z 790 [M+Na]; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (3H, *d*, J = 8, C-18H_3), 1.16 (3H, *s*, C-16H_3), 1.26 (3H, *s*, C-17H_3), 1.42 (9H, *s*, Boc), 1.61 (3H, *s*, C-19H_3), 1.80 (1H, *m*, C-11H), 2.00 (2H, *m*, C-6H_2 et C-14H_2), 2.42 (1H, *m*, C-6H_2), 2.63 (1H, *m*, C-12H), 2.74 (1H, *d*, J = 16, C-14H_2), 3.72 (1H, *d*, J = 8, C-3H), 4.01 (1H, *m*, C-7H), 4.03 (1H, *d*, J = 8, C-20H_2), 4.50 (1H, *d*, J = 8, C-20H_2), 4.73 (1H, *m*, C-5H), 4.80 (1H, *bs* , C-2'H), 5.00 (1H, *m*, C-10H), 5.32 (1H, *bs* C-3'H), 5.41 (1H, *m*, C-13H) , 5.72 (1H, *d*, J = 8, C-2H), 5.84 (1H, NH), 7.36 (5H, Ph), 7.47-7.61-8.00 (5H, OBz); ^{13}C NMR (62 MHz, $CDCl_3$) δ 9.46 (C-18H_3), 15.80 (C-19H_3), 25.41 (C-16H_3), 28.42 (C-BocH9), 32.15 (C-12H), 32.38 (C-17H_3), 34.81 (C-14H_2), 35.40 (C-6H_2), 40.47 (C-3H), 42.38 (C-15), 56.93 (C-8/C-3'H), 60.26 (C-11H), 69.70 (C-7H), 70.29 (C-10H), 73.82 (C-2H/C-13H), 75.22 (C-2'H), 75.55 (C-4 or C-1), 78.60 (C-1 or C-4), 80.89 (C-20H_2/Cq-Boc), 86.52 (C-5H), 126.95-128.07-128.85-138.63 (C-3'Ph), 129.06 (CH-*m* Bz), 129.36 (Cq Bz), 129.93 (CH-*o* Bz), 133.97 (CH-*p*Bz), 154.32 (CO Boc), 166.91 (COPh), 171.58 (C-1'), 208.05 (C-9).

15: IR ($CHCl_3$) 3431, 1718, 1706 cm^{-1}; FABMS m/z 790 [M+Na]; ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (3H, *d*, J = 8, C-18H_3), 1.03 (3H, *s*, C-16H_3), 1.16 (3H, *s*, C-17H_3), 1.39 (9H, *s*, Boc), 1.67 (3H, *s*, C-19H_3), 1.79 (1H, *dd*, C-11H), 2.04 (1H, *m*, C-14H_2), 2.24 (1H, *m*, C-6H_2), 2.31 (1H, *m*, C-6H_2), 2.58 (1H, *m*, C-12H), 2.80 (1H, *d*, J = 16, C-14H_2), 3.81 (1H, *m*, C-7H), 3.87 (1H, *d*, J = 8, C-3H), 4.09 (1H, *d*, J = 8, C-20H_2), 4.59 (1H, *d*, J = 8, C-20H_2), 4.66 (1H, *d*, J = 5, C-2'H), 4.76 (1H, *m*, C-5H), 5.13 (1H, *s large*, C-3'H), 5.24 (1H, *m*, C-10H), 5.47(1H, *m*, C-13H), 5.51 (1H, NH), 5,72 (1H. *d*, J = 8, C-2H), 7.33 (5H, *m*, Ph), 7.45-7.55-8.06 (5H, OBz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.03 (C-18H_3), 17.28 (C-19H_3), 25.21 (C-16H_3), 28.48 (C-BocH9), 32.40 (C-17H_3), 32.73 (C-12H), 35.21 (C-14H_2), 36.04 (C-6H_2), 38.80 (C-3H), 40.51 (C-15), 54.97 (C-8), 57.47 (C-3'H), 60.60 (C-11H), 74.20 (C-2H/C-13H), 75.32 (C-10H), 76.27 (C-2'H), 78.29 (C-7H),78.62 (C-4 ou C-1), 79.87 (C-1 ou C-4), 81.38 (C-20H_2/Cq-Boc), 86.23 (C-5H), 127.37-128.34-128.84-137.66 (C-3'Ph), 129.0 (CH-*m* Bz), 130.08 (Cq Bz), 130.23 (CH-*o*Bz), 133.80 (CH-*p*Bz), 156.22 (CO Boc), 166.75 (COPh), 170.36 (C-1'), 209.41 (C-9).
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20. The compounds considered as inactive on the disassembly process of microtubules into tubulin are those for which the IC_{50} can not be reach. In the taxoid series, this corresponds to a concentration superior to about 10^{-4}M.
21. This compound was obtained quantitatively from 7-SiEt3-10-deacetylbaccatin III after selective reduction at C-4 with Super-hydride. Coupling of the 4-deacetyl derivative with the acid side chain **6** (76%) followed by acidic deprotection (41%) afforded 4-deacetydocetaxel. 4-Deacetyldocetaxel and 4-deacetylpaclitaxel have been synthesized by others teams (see for example Ref 11 and 12).

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