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A NEW REARRANGEMENT OF OXETANE-TYPE TAXOIDS [1]

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Abstract: *Treatment of 7-triethylsilyl-14β-hydroxy-10-deacetylbaccatin III (**1b**) with pyridinium p-toluenesulfonate in refluxing benzene gave the orthoester **3** as a result of O(2) → O(14) benzoate migration, contraction of ring A followed by formation of an ether bridge between C(15) and C(10), and rearrangement of the 4-acetoxy-5(20)-oxetane moiety into a C(5)-epimerized 2,4,20-orthoacetate.*

The development of second generation antitumor taxoids based on a diterpene core different from baccatin III is an area of considerable current interest.[2] In this context, taxol analogues functionalized at C-14 have emerged as very promising anticancer agents.[3] The synthesis of these compounds uses 14β-hydroxy-10-deacetylbaccatin III (**1a**) as starting material.[3] **1a** is a by-product of the isolation of 10-deacetylbaccatin III (**2a**) from the needles of several yew species,[4] and thus its supply poses no extra ecological burden on plants from the genus *Taxus*.[5]

One of the advantages of the 14-functionalized system over the parent one, is a major stability in protic solvents towards the acid-catalysed opening of the oxetane ring.[6] This is an important asset for the chemical elaboration of **1a**. We now report the surprising observation that in apolar solvents this order of stability is reversed. Indeed, the combined activity of mild acidic conditions and heating can trigger a deep-seated rearrangement of some derivatives of **1a**, ultimately leading to the unprecedented reorganization of the acyl-substituted oxetane ring into an orthoester and overall affecting nine carbons of the diterpenoid core.

When 7-triethylsilyl(Tes)-14β-hydroxy-10-deacetylbaccatin III (**1b**)[7] was refluxed in benzene in the presence of catalytic amounts (0.05 mol. equiv.) of pyridinium *p*-toluenesulfonate (PPTS), rapid disappearance (*ca* 60 min) of the starting material took place, and the less polar compound **3** was isolated in *ca* 40% yield.[8] The 7,14-diTes derivative of **1a** (compound **1c** [9]), was stable under these reaction conditions, whereas the 7-Tes derivative of 10-deacetylbaccatin III (compound **2b** [10]) gave the *abeo*taxane **4**[11] in ca 50% yield.

Mass spectrometry showed a molecular weight of 656 for **3**, corresponding to the molecular formula $C_{35}H_{48}O_{10}Si$ and to the overall loss of one water molecule from **1b**. Comparison of the NMR features of **3** and **1b** showed the disappearance of the acetate signals at 2.31 ppm (^{1}H-spectrum) and 170.3 ppm (^{13}C-spectrum), that were replaced by singlets at 1.50 ppm and 118.9 ppm respectively. These data suggested the presence of an orthoacetate group,[12] and contraction of ring A was also evident from the presence of a singlet at 64.57 ppm for C(1) in the ^{13}C NMR spectrum.[13] Connectivity analysis via COSY and proton-carbon correlation allowed to assign all the proton and carbon resonances. Epimerization at C(5) was evidenced by the multiplicity of H-5 (br

s),[14] whereas the downfield chemical shift of H-14 (5.75 ppm) showed that the benzoate had migrated from O(2) to O(14).[6] Experiments of *in situ* acylation with trichloroacetyl isocyanate (TAI)[15] disclosed the presence of only two hydroxyls, that were located at C(5) and C(13) on account of the paramagnetic shifts undergone by these protons ($\Delta\delta$ + 1.15 and + 1.28 ppm respectively). Thus, the remaining four oxygens were all part of ether-like bonds. These data could be rationalized by the formation of an ether bridge between C(10) and C(15), and of an orthoester between C(2), C(4) and C(20).

A plausible mechanism for the rearrangement of **1b** to **3** is depicted in scheme 1. Migration of the benzoate to O(14), presumably via 1,2 and 1,14 dioxolanylium ions, triggers the Wagner-Meerwein rearrangement of ring A and the acetate - assisted opening of the oxetane ring,[14] eventually giving the stable orthoacetate **3**. In **1c** and **2b**, where O(2)→O(14) acyl migration is not possible, oxetane-cleavage did not take place under these mild conditions. This shows that opening of the oxetane by the neighbouring acetyl is catalysed by the C(2) hydroxyl, presumably *via* trapping of a 4,20-dioxolanylium ion [14c] (see scheme 1).

In baccatin III derivatives, oxetane opening by the C(2) hydroxyl via base-catalysed SN2-type attack on C(20) and formation of a 2,20-ether had already been observed.[16] The different mode of oxetane cleavage in **1b** is presumably related to the reaction conditions (pH, solvent), and not to the skeletal rearrangement of ring A. Models show in fact that the O(2) - C(20) distance is not significantly affected by contraction of ring A and formation of the C(10)-C(15) oxygen bridge. In the absence of coordinative solvents, intramolecular stabilization of cationic intermediates by oxygen functions *via* dioxolanylium ions or orthoester formation might be the major factor allowing the smooth rearrangement of **1b** to **3**. Indeed, when the reaction mixture obtained refluxing **1b** and PPTS in polar solvents (methanol, acetone) was scrutinized for the presence of **3** or its 7-desilylated product, none was found.[17]

Acyl migration,[18] ring A contraction[14] and oxetane cleavage[14, 16] are well precedented in taxoids, but the rearrangement of **1b** to **3** combines them in an original mode, that highlights the subtle interplay of the various oxygenated groups in these densely functionalized compounds.

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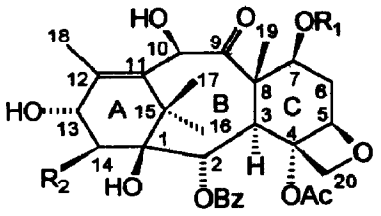
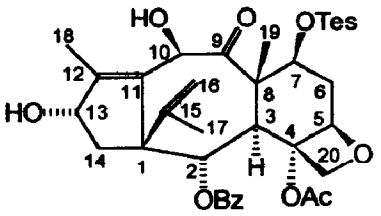
7. Prepared in 82% yield by treatment of **1a** with Tes-Cl (2 mol. equiv.) and imidazole (2 mol. equiv.) in DMF.
8. The reaction mixture was diluted with EtOAc, washed with sat. aq. $NaHCO_3$ and evaporated. The residue was purified by CC (silica gel, hexane-EtOAc 5:5 as eluant) to give **3** as a white powder, m.p. 70°; $[\alpha]_D^{25}$ -97 ($CHCl_3$, *c* 0.53); UV λ_{max} (EtOH): 281, 228 nm; IR ν_{max} (KBr): 3440, 1710, 1600, 1280, 1120, 1010, 850, 715 cm^{-1}; CI-MS (NH_3): 674 $(M + NH_4)^+$ ($C_{35}H_{48}O_{10}Si$ +



	R_1	R_2
1a	H	OH
1b	Tes	OH
1c	Tes	OTes
2a	H	H
2b	Tes	H



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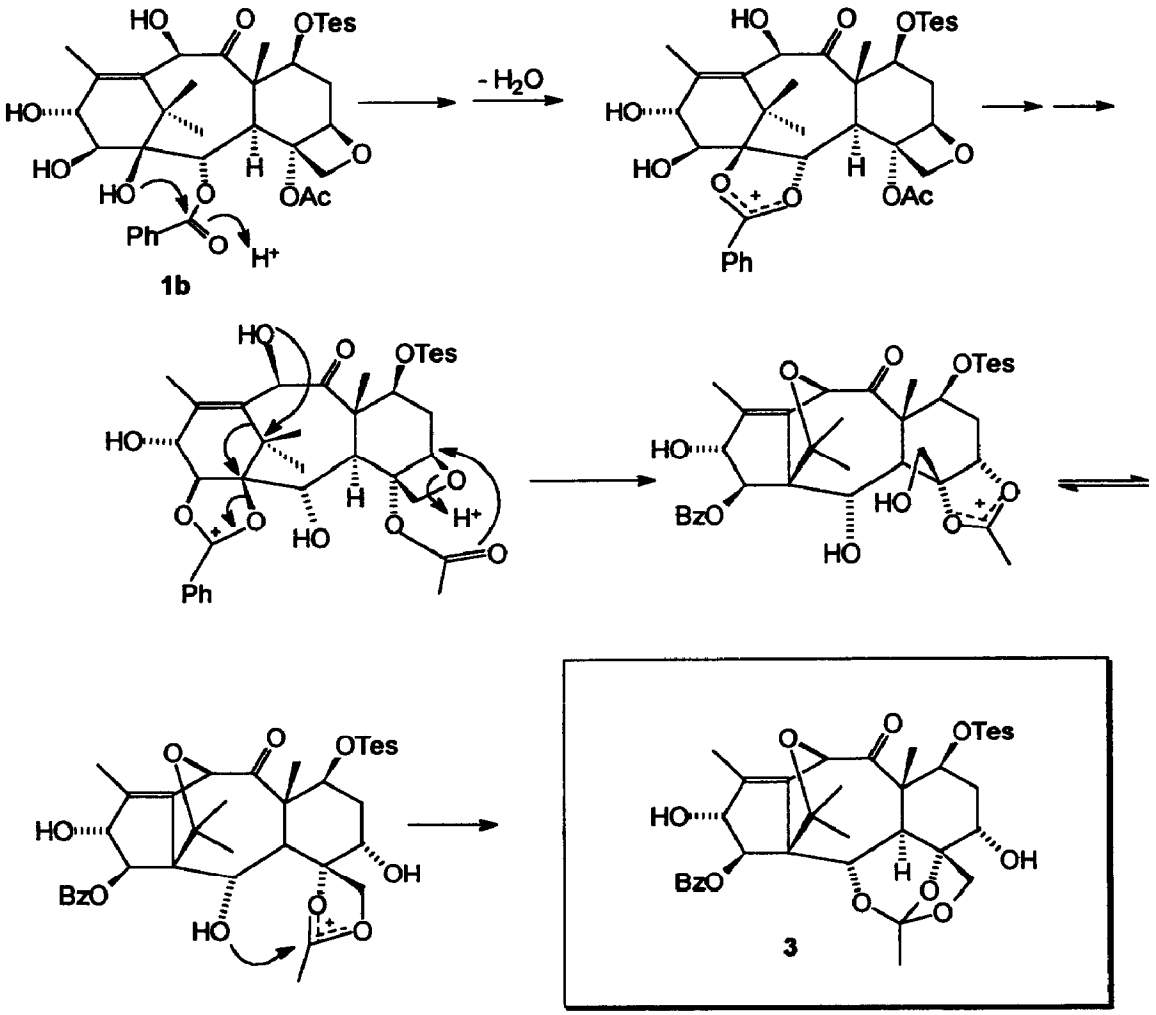
SCHEME 1



$NH_4)^+$(100); ^1H NMR (400 MHz, $CDCl_3$, TMS as reference): δ 7.99 (d, J=7.6 Hz, Bz), 7.63 (t, J=7.6 Hz, Bz), 7.49 (t, J=7.6 Hz, Bz), 5.75 (d, J= 4.0 Hz, H-14), 5.14 (d, J=11.0 Hz, H-2), 4.76 (s, H-10), 4.64 (dd, J= 11.9, 4.9 Hz, H-7), 4.51 (d, J=7.9 Hz, H-20a), 4.48 (br t, J= 4.0, H-13), 3.81 (br s, H-5), 3.41 (d, J=7.9, H-20b), 2.32 (d, J= 11.0 Hz, H-3), 2.05 (m, H-6α), 1.88 (br s, H-18), 1.79 (s, H-16), 1.50 (s, orthoacetate), 1.41 (m, H.6β), 1.40 (s, H-19), 1.26 (s, H-17), 0.94 (t, J= 8.0 Hz, Tes), 0.64 (m, Tes); ^{13}C NMR (100 MHz, $CDCl_3$, TMS as reference): δ 203.90 (s, C-9), 168.05 (s, Bz), 139.08 (s, C-12), 138.27 (s, C-11), 133.54 (d, Bz), 129.58 (d, Bz), 129.46 (s, Bz), 128.68 (d, Bz), 118.93 (s, orthoacetate), 86.03 (d, C-13), 85.50 (s, C-15), 83.12 (s, C-4), 83.05 (d, C-14), 80.49 (d, C-10), 70.76 (d, C-5), 70.32 (d, C-2), 69.79 (t, C-20), 66.91 (d, C-7), 64.57 (s, C-1), 53.26 (s, C-8), 36.43 (d, C-3), 34.22 (t, C-6), 25.31 (q, C-17), 22.64 (q, C-16), 21.65 (q, orthoacetate), 12.17 (q, C-18), 11.70 (q, C-19), 7.01 (q, Tes), 5.22 (t, Tes).

9. Prepared in 91% yield by treatment of **1a** with Tes-Cl (60 mol. equiv.), triethylamine (60 mol. equiv.) and DMAP (2.7 mol. equiv.) in CH_2Cl_2.
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11. White powder, m.p. 145 °, $[\alpha]_D^{25}$ -144 ($CHCl_3$, *c* 0.45); UV λ_{max} (EtOH): 280, 229 nm; IR ν_{max} (KBr): 3440, 1725, 1610, 1280, 1245, 1120, 1080, 720 cm^{-1}; CI-MS (NH_3): 658 $(M + NH_4)^+$ $(C_{35}H_{48}O_9Si + NH_4)^+$ (100); ^1H NMR (400 MHz, $CDCl_3$, TMS as reference): δ 8.00 (d, J=7.6 Hz, Bz), 7.67 (t, J=7.6 Hz, Bz), 7.46 (t, J=7.6 Hz, Bz), 5.58 (d, J=7.8 Hz, H-2), 5.21 (s, H-10), 5.04 (d, J=8.8 Hz, H-5), 4.92 (br s, H-16a), 4.69 (br s, H-16b), 4.63 (m, H-13), 4.40 (dd, J=10.7, 4.8 Hz, H-7), 4.30 (d, J=7.6 Hz,H-20a,), 4.23 (d, J=7.6 Hz, H-20b), 3.59 (d, J=7.8 Hz, H-3), 2.41 (m, H-6α), 2.19 (m, H-14a), 2.27 (s, Ac), 1.98, 1.59 (br s, H-17 and H-18), 1.78 (s, H-19), 0.93 (t, J=8.0 Hz, Tes), 0.53 (m, Tes). ^{13}C NMR (100 MHz, $CDCl_3$, TMS as reference): δ 209.76 (s, C-9), 170.51 (s, Ac), 165.30 (s, Bz), 147.43 (s, C-12), 145.51 (s, C-11), 137.30 (s, C-15), 133.53 (d, Bz), 129.72 (d, Bz), 129.41 (s, Bz), 128.60 (d, Bz), 112.36 (t, C-16), 84.86 (d, C-5), 79.06 (s, C-4), 75.95 (d, C-10), 74.55 (t, C-20), 72.93 (d, C-7), 70.98 (d, C-2), 69.82 (d, C-13), 63.85 (s, C-1), 56.26 (s, C-8), 44.34 (d, C-3), 42.02 (t, C-14), 38.21 (t, C-6), 21.89 (q, Ac), 20.81 (q, C-17), 11.23 (q, C-18), 9.02 (q, C-19), 6.71 (q, Tes), 5.00 (t, Tes).
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