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Acid and Base Catalysed Rearrangements of 9,10-Dioxotaxanes[1]

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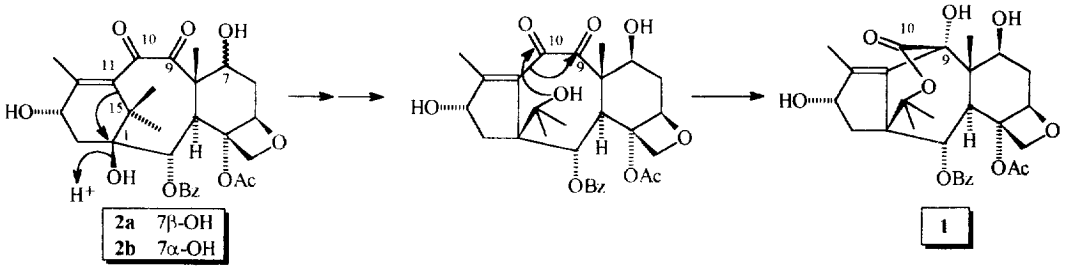
Abstract: *Treatment of 10-dehydro-10-deacetylbaccatin III (**2a**) with trichloroacetic acid gave the bis-abeotaxane **3**, whereas treatment of **2a** and its 7-epimer (**2b**) with bases (DBU, NaH) triggered a tandem retroaldol-Michael reaction, giving a compound of the 7,8-seco-8,12-cyclotaxane type. Both skeletal rearrangements were accompanied by extensive reorganisation of the oxygen functions in the southern hemisphere of the molecule.*

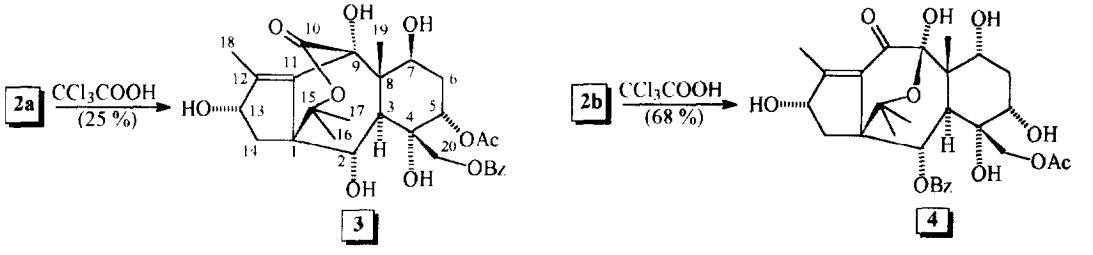
The growing inventory of rearranged and unusually functionalized taxanes[2] has spurred research in the development of non-enzymatic mimics of their biogenesis.[3] In this context, our interest was piqued by the unique 11(15→1),11(10→9)bisabeotaxane structure of wallifoliol (**1**), a constituent of the needles of the Himalayan yew.[4] **1** is formally derived from a tandem Wagner-Meerwein \ benzil-benzilic acid-type rearrangement of 10-dehydro-10-deacetylbaccatin III (**2a**) (Scheme 1), and we report here our attempts to mimic this complex reaction.



*Scheme 1. Possible biogenetic relationship between wallifoliol (**1**) and 10-dehydro10-deacetylbaccatin III (**2a**)*

Treatment of **2a**[5] under a variety of acidic conditions gave mixtures of products, which were monitored by ^{13}C-NMR spectroscopy for the presence of a lactone carbonyl signal around δ 175, a feature typical of C-10 of wallifoliol-type compounds.[4] A signal of this type was present in the trichloroacetic acid - CH_2Cl_2 reaction mixture. After considerable optimisation of the reaction time and the concentration of the acid, the bis-abeotaxane **3** was obtained in *ca* 25% yield (Scheme 2).[6] The molecular formulae of **1** and **3** differed for the

presence of an additional water molecule in **3** ($C_{29}H_{36}O_{11}$). The appearance of C-10 as a lactone carbonyl (δ 174.0, s) and C-15 as a deshielded singlet at δ 89.8 showed that **3** had the same lactone-bridged bis-abeotaxane skeleton of wallifoliol. However, comparison of the ^{1}H-NMR spectra showed changes in the southern hemisphere. Indeed, H-2 was shifted upfield in **3** (Δδ -1.36), whereas the acetyl methyl and H-5 underwent a downfield shift (Δδ + 0.38 and +0.31 respectively), and $J_{20a,b}$ increased (in absolute value) from 7 Hz in **1** to 12 Hz in **3**. The rearrangement of the oxygenated functions could be rationalised in terms of acetate-assisted opening of the oxetane ring, a well-known reaction of baccatin III-type taxoids,[7] followed by migration of the benzoate at the 20-hydroxyl. The location of the ester groups was confirmed by the detection of long-range ^{1}H-^{13}C correlations (HMBC) between H-5 and the acetate carbonyl (δ 170.3) and H-20a,b and the benzoate carbonyl (δ 166.7). Under these conditions, **2b**,[5] the C-7 epimer of **2a**, did not give bisabeotaxanes, but the 11(15→1)abeotaxane **4**, resulting from the attack of the C-15 tertiary hydroxyl to the 9-carbonyl and a different reorganisation of the oxygen functions in the southern hemisphere.[8] The regiochemistry of the attack on the 9,10-dioxo system thus depends on the configuration of the hydroxyl at C-7, presumably as a result of the formation in **2a** of a strong intramolecular hydrogen bonding between the 7β-hydroxyl and the 9-carbonyl. This favours a conformation of ring B that places the 15-hydroxyl close and ideally oriented [9] to attack the 10-carbonyl. The fact that wallifoliol-type compounds were not obtained during the acidic rearrangement of **2b** implies an alternative conformation, favouring instead in terms of proximity and orientation the attack on the 9-carbonyl.[10]

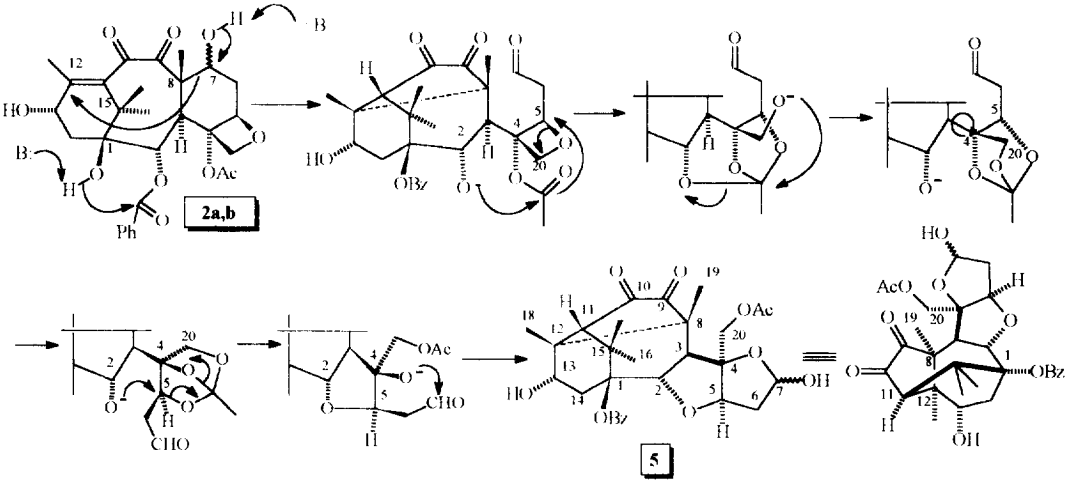


Scheme 2. Acid catalysed rearrangement of ***2a*** *and* ***2b***

The benzil-benzilic acid rearrangement normally takes place in basic medium, but in these conditions baccatin III derivatives undergo retro-aldol equilibration.[11] In the case of **2a,b**., this triggers a most remarkable rearrangement of the carbon skeleton and oxygen functions, resulting in the formation of the 7,8-seco-8,12-cyclotaxane **5**.[12] In basic medium, retroaldolization is followed (Scheme 3) by the Michael addition of the 8-enolate to the enone system, whereas benzoate migration at the C-1 hydroxyl unleashes the reorganisation of the acetoxyoxetane moiety into a 4,5,20-orthoester.[13] The latter then evolves into a C-2,C-5 ether, and formation of a five-membered hemiacetal ring between the hydroxyl at C-4 and the C-7 aldehyde terminates the reaction. The marvellous complexity of the rearrangement is complemented by a very high yield (84%) and mild reaction conditions (treatment with catalytic amounts of NaH or DBU at room temperature)[14]

5 was obtained as a 85:15 mixture ($CDCl_3$ ratio) of anomers. The new carbon connectivity was evident from the appearance of a singlet at δ 2.02 for H-11 and a sharp signal, showing a long-range ^{1}H-^{13}C correlation with C-8, for H-18 (δ 1.09). In the ^{13}C NMR spectrum, the olefinic signals were replaced by an aliphatic methine at δ 59.1 (C-11) and a quaternary carbon at δ 43.0 (C-12). The establishment of the oxygen connectivity in the southern part of the molecule relied on the following observations: the benzoate carbonyl showed no long-range correlation with protons of the terpenoid core, indicating that it was bound to a tertiary hydroxyl. The presence of NOE-effects between the geminal methyls and the benzoate *ortho*-protons, and the downfield resonance of H-14a,b (δ 3.53 and 2.91 respectively) located the benzoate at C-1. The molecular formula of **5** ($C_{29}H_{34}O_{10}$) required two extra unsaturations, accounted for by a lactol ring (δ 100.5, d, C-7) and an ether bridge. Among the possible combinations, that depicted in **5** was supported by the detection of a long-range correlation between H-5 and C-2 (C-2, C-5 ether) and H-7 and C-4 (C-4, C-7 hemiacetal). The presence of the furo-furanose system

was further supported by the NOE experiments (correlations H-5 / H-20a,b; H-5 / acetate and H-19 / H20a,b).[15] The detection of a NOE-effect between the acetate and H-7 showed that the major anomer in $CDCl_3$ has a β-oriented hemiacetal hydroxyl.[16]



Scheme 3. Base catalysed rearrangement of **2a,b** *(B DBU, NaH; yield 80-90%)*

The rearrangement of **2a,b** to **5** involves an unprecedented degree of reorganisation of the carbon and oxygen connectivity, and shows how much more we still have to learn about the subtleties of the chemistry of taxoids.

REFERENCES AND NOTES

1. Part XXIV in the series: The Chemistry and Occurrence of Taxane Derivatives. For part XXIII, see reference 3. This paper is dedicated to the memory of Pierluigi Gariboldi, with whom we would have loved to share the excitement of natural products research for a much longer time.
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6. To a solution of **2a** (200 mg, 0.37 mmol) in CH_2Cl_2 (5 ml), trichloroacetic acid (330 mg, 2.0 mmol, 5.4 quiv.) was added. After stirring at room temp. for 15 h, the reaction was worked up by dilution with EtOAc and washing with $NaHCO_3$. After removal of the solvent, the residue was purified by CC (hexane-EtOAc 3:7) to give 54 mg (25%) **3**. CI-MS (NH_3): 578 $(M + NH_4)^+$ $(C_{29}H_{36}O_{11} + NH_4)^+$ (55). ^1H NMR (400 MHz, acetone-d_6, TMS as reference): δ 8.10 (br d, J=7.7 Hz, Bz), 7.64 (br t, J=7.7 Hz, Bz), 7.50 (br t, J=7.7 Hz, Bz), 5.18 (br t, J=3.8 Hz, H-5), 4.78 (d, J=12.0 Hz, H-20a), 4.53 (d, J=12.0Hz, H-20b), 4.47 (t, J=6.5 Hz, H-13), 4.45 (d, J=11.5 Hz, H-2), 4.18 (dd, J= 10.0, 6.5 Hz, H-7), 2.43 (d, J=11.5 Hz, H-3), 2.16 (dd, J=16.0, 6.5 Hz, H-14a), 2.03 (br s, H-18), 2.00 (s, Ac), 1.40 (s, H-16), 1.14 (s, H-17), 1.11 (s, H-19). ^{13}C NMR (100 MHz, acetone-d_6, TMS as reference): δ 174.0 (s, C-10), 170.3 (s, Ac), 166.7 (s, Bz), 139.7 (s, C-12), 134.0 (d, Bz), 132.6 (s, Bz), 130.9 (s, C-11), 130.5 (d, Bz), 129.4 (d, Bz), 89.8 (s, C-15), 85.1 (s, C-9), 79.6 (d, C-13), 76.4 (s, C-4), 71.6 (d, C-5), 69.0 (d, C-2 + C-7), 67.1 (t, C-20), 62.2

(s, C-1), 48.7 (s, C-8), 46.2 (d, C-3), 36.2 (t, C-14), 33.5 (t, C-6), 25.3 (q, C-17), 23.2 (q, C-16), 21.1 (q, Ac), 12.1 (q, C-9), 11.0 (q, C-18). The ^{1}H and ^{13}C NMR spectra of **3** and **5** were assigned with the aid of NOE-inspection and the HMBC spectra.

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9. To avoid electrostatic repulsion by the oxygen lone-pairs, nucleophiles approach a carbonyl group at an angle of about 107° (Bürgi, H.B.; Dunitz, J.D.; Shefter, E. *J. Am. Chem. Soc.* **1973**, *95*, 5065-5067).
10. Models show that the attack to the C-10 carbonyl is favoured by a negative torsion angle around C-9, C-10, whereas a positive torsion angle C-9, C-10 favours attack to the C-9 carbonyl.
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12. The bidimensional representation of **5** was done according to the Lythgoe convention, that is, the substituents at the bridgehead carbons (C-1, C-8, C-11, C-12) are considered as cyclooctane ring B substituents (Eyre, D.H.; Harrison, J.W.; Lythgoe, B. *J. Chem. Soc. (C)* **1967**, 452-462). For sake of clarity, an alternative and unambiguous representation is also given in Scheme 3. Note that the stereochemical descriptors of the substituents at C-1, C-8, C-11, and C-12 are inverted. For a discussion of the bidimensional representation of taxoids, see: Appendino, G. in *The Chemistry and Pharmacology of Taxol® and its Derivatives*; Farina, V. Ed.; Elsevier, 1995; pp. 13-18.
13. For the rearrangement of a baccatin III derivative into a stable 2,4,20-orthoester, see: Appendino, G.; Varese, M.; Gariboldi, P.; Gabetta, B. *Tetrahedron Lett.* **1994**, 2217-2220.
14. Reaction with **2a** as representative: a solution of **2a** (500 mg) in toluene (20 ml) was treated with DBU (200 µl) and stirred at room temp.. After 24 h the reaction mixture was washed with dil HCl and brine. The residue, a yellowish powder, was purified by CC (hexane-EtOAc 6:4) to give 420 mg (84%) **5**. CI-MS: 560 $(M + NH_4)^+$ $(C_{29}H_{34}O_{10} + NH_4)^+$ (100). ^{1}H NMR (400 MHz, $CDCl_3$, TMS as reference, resonances of the major anomer): δ 7.93 (br d, J=7.7 Hz, Bz), 7.52 (br d, J=7.7 Hz, Bz), 7.41 (br t, J=7.7 Hz, Bz), 5.55 (d, J=6.0 Hz, H-7), 4.62 (d, J=12.0 Hz, H-2), 4.54 (d, J=6.8 Hz, H-5), 4.45 (d, J=12.0 Hz, H-20a), 4.42 (dd, J=10.5, 5.0 Hz, H-13), 4.22 (d, J=12.0 Hz, H-20b), 3.53 (dd, J=15.0, 5.0 Hz, H-14a), 2.91 (dd, J=15.0, 10.5 Hz, H-14b), 2.90 (d, J=12.0 Hz, H-3), 2.11 (ddd, J=15, 7.0, 6.0 Hz, H-6a), 2.04 (s, Ac), 2.02 (s, H-11), 1.84 (d, J=15 Hz, H-6b), 1.50 (s, H-19), 1.44 (s, H-17), 1.33 (s, H-16), 1.09 (s, H-18). ^{13}C NMR (100 MHz, $CDCl_3$, TMS as reference, resonances of the major anomer): δ 206.2 (s, C-9), 201.8 (s, C-10), 170.2 (s, Ac), 165.7 (s, Bz), 132.6 (d, Bz), 131.8 (s, Bz), 129.6 (d, Bz), 128.3 (d, Bz), 100.5 (d, C-7), 94.5 (s, C-4), 84.7 (d, C-5), 83.8 (s, C-1), 78.1 (d, C-2), 72.7 (d, C-13), 67.6 (t, C-20), 59.1 (d, C-11), 53.2 (d, C-3), 52.8 (s, C-8), 43.7 (s, C-12), 43.6 (s, C-15), 41.1 (t, C-6), 38.3 (t, C-14), 28.8 (q, C-16), 28.0 (q, C-18), 21.1 (q, C-17), 20.8 (q, Ac), 18.4 (q, C-19).
15. The H-5/H-20a,b NOE correlations are especially relevant. They show that the rearrangement takes place with an overall retention of configuration at C-5, implying two Sn2-type displacements (see Scheme 3). The *cis*-relationship between the 19-methyl and H-20a,b is evidenced in the alternative representation of **5**.
16. The ratio between the anomers varied with the solvent, and in DMSO-d_6 was *ca* 1:1. Acetylation of **5** afforded an easily separable mixture of anomeric acetates in a *ca* 1:1 ratio.

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