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The Synthesis of A-Nor-B-homobaccatin III Derivatives[1]

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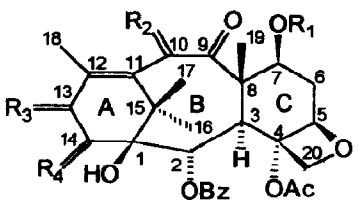
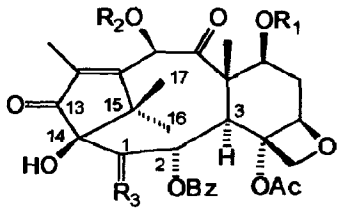
Abstract: *Treatment with activated MnO_2 of 7-protected derivatives of 10-deacetylbaccatin III and 14β-hydroxy-10-deacetylbaccatin III gave A-nor-B-homotaxoids resulting from α-ketol rearrangement of 13,14-dioxotaxane intermediates.*

7-Trietylsilyl(TES)-10-deacetylbaccatin III (**1a**) is an important intermediate for the hemisynthesis of the anticancer drug taxol,[2] and has been extensively used as a starting material for the synthesis of new antitumor taxoids.[3] As part of a study aimed at the systematic modification of the various functional groups of 10-deacetylbaccatin III (**1b**), we investigated the MnO_2 oxidation of **1a**. The reaction gave a mixture of the 13-dehydroderivative (**1c**) and a less polar and further oxidized product, whose ratio depended on the reaction time and the excess of oxidant.[4,5] A similar behaviour was observed with **1b**. However, the structure of the more oxidized products was completely different. **1b** gave **1d**, the result of the oxidation of both allylic hydroxyls, whereas a more complex reaction took place with **1a**. Indeed, the ^1H NMR spectrum of the more oxidized product from the reaction of **1a** still displayed the signal of H-10 (δ 5.85, d, $J_{10,OH}$ = 3.5 Hz), whereas the A,B-system of H-13 and H-14 had disappeared. Comparison with the ^{13}C NMR spectrum of the starting material showed that two oxymethine carbons were missing, replaced by two carbonyl resonances (δ 200.3 and 199.1). These data were compatible with the α-diketone structure **1e**. However, some spectroscopic features were unusual for the structure **1e**, and pointed instead to the alternative structure **2a**.[6] The carbon bearing the tertiary hydroxyl (C-1 in **1e**, C-14 in **2a**) resonated in fact at very low field (δ 98.2) for a mono-oxygenated quaternary carbon, and the chemical shift of the enone β-carbon (C-11, δ 173.2) was more typical of a cyclopentenone rather than a cyclohexenone.[7] Furthermore, the small value of $J_{2,3}$ (1.0 Hz) and the downfield chemical shift of C-15 (δ 50.4) were unusual for baccatin III derivatives,[8] whereas the long-wavelength absorption band of the ring A enone (λ_{max} 270 nm) was significantly different from the value reported in 14-oxotaxinine (λ_{max} 284 nm),[9] in spite of a similar ring-A chromophore and the expected bathochromic shift (*ca* 7 nm) of the hydroxyl at C-1[10]

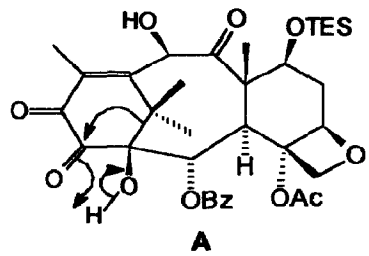
Ring A contraction and ring B expansion as in **2a** could nicely rationalize this data, owing to the deshielding effect of two α-carbonyls on the carbon bearing the tertiary hydroxyl (C-14), and to a major flexibility of ring B, allowing deviation from the topology typical of baccatin III derivatives. The rearranged structure **2a** was further confirmed by the detection (HMBC spectrum) of a long-range (^{3}J) correlation between H-3 and the carbonyl resonance at δ. 200.3 (C-1).[11]





	R_1	R_2	R_3	R_4
1a	TES	αH, βOH	αOH, βH	H, H
1b	H	αH, βOH	αOH, βH	H, H
1c	TES	αH, βOH	=O	H, H
1d	H	=O	=O	H, H
1e	TES	αH, βOH	=O	=O
1f	TES	αH, βOH	αOH, βH	αH, βOH
1g	TROC	αH, βOTROC	αOH, βH	H, H
1h	TROC	αH, βOTROC	αOH, βH	αH, βOH

	R_1	R_2	R_3
2a	TES	H	=O
2b	TES	H	αOH, βH
2c	TROC	TROC	=O



A

To confirm the unprecedented structure of **2a**, this compound was reduced with $NaBH_4$ to the vicinal diol **2b**.[12] The splitting pattern of H-2 in **2b** (dd, $J_{1,2}$=2.5 Hz, $J_{2,3}$=1.5 Hz) showed coupling with two protons, thus locating the site of hydride attack to an adjacent carbon. Furthermore, a long-range (^{3}J) corelation between H-1 and C-3 was observed in the HMBC spectrum. The α-stereochemistry of the C-1 hydroxyl and the *cis*-relationship between H-1 and H-2 were evidenced by the detection of strong NOE-effects between H-1 and H-16 (6%), H-2 and H-16 (15%), and H-1 and H-2 (7%).

The obtaining of **2a** from **1a** presumably involves the formation of the α-diketone **1e**, which undergoes an α-ketol rearrangement (**A**) opposite to that described by Paquette in his synthesis of taxane analogues via an oxy-Cope approach.[13] The driving force for the α-ketol rearrangement might be the release of the angular strain due to the presence of four adjacent sp^2 carbons in the anti-Bredt olefin **1e**, as well as the release of steric strain around the heavily substituted cyclooctanone B-ring. We have been unable to obtain **1e** from an independent synthesis, and the role of MnO_2 in the rearrangement is thus unknown. **2a** might be formed from the 13-dehydro

derivative **1c** via oxidation of the activated methylene, a type of reaction very rare, but not unprecedented,[14] with MnO_2.

Rearranged product **2a** was also obtained (35 % yield) from the oxidation of the 7-TES derivative of 14β-hydroxy-10-deacetylbaccatin III (**1f**),[15] whereas the 7,10-di-TROC (2,2,2-trichloroethoxycarbonyl) derivatives of 10-deacetylbaccatin III and 14β-hydroxy-10-deacetylbaccatin III (compounds **1g** and **1h** respectively) gave the rearranged product **2c** [16] (yield 41% and 39 % respectively) along with the corresponding 13-dehydroderivatives.

Comparison of the reactivity of **1a** and **1b** toward MnO_2 shows that silylation of the C-7 hydroxyl prevents the oxidation of the allylic C-10 hydroxyl, activating an unusual functionalization of the C-14 methylene. Remarkable differences had already been observed in the methanolysis[17] and the SmI_2 deoxygenation[18] of the corresponding C-10 acetates. Also in these cases, the reactivity of the C-10 oxygen function was shut down by silylation of the C-7 hydroxyl. This intriguing effect highlights the subtleties of taxane chemistry, whose rationalization provides unique challenges to natural product chemists.

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REFERENCES AND NOTES

1. Part XVIII in the series: The Chemistry and Occurrence of Taxane Derivatives. For part XVII, see: Barboni, L.; Gariboldi, P.; Appendino, G.; Enriù, R.; Gabetta, B.; Bombardelli, E. *Liebigs Ann. Chem.* (submitted for publication).
2. Denis, J.D.; Greene, A.E.; Guénard, D.; Guéritte-Voegelein, F.; Mangatal, L.; Potier, P.; *J. Am. Chem. Soc.* **1988**, *110*, 5197-5199.
3. Chen, S.-H.; Huang, S.; Gao, Q.; Golik, J.; Farina, V. *J. Org. Chem.* **1994**, *59*, 1475-1484 and references therein.
4. Typical reaction procedure: to a solution of **1a** (1.0 g, 1.48 mmol) in 25 ml EtOAc-CH_2Cl_2 (9:1), activated MnO_2 (Merck, 10 g) was added, and the reaction was stirred at room temp. for 24 h and then filtered over celite. The residue was separated by CC (silica gel, hexane-EtOAc 8:2 as eluant) to give 248 mg (24 %) **2a** and 398 mg (40 %) **1c**. **2a**: white powder, m.p. 80°; UV λ_{max} (EtOH) (log ε): 300 (sh), 270 (3.6), 232 (4.4); IR ν_{max} (KBr): 3450, 1740, 1710, 1620, 1270, 1260, 1235, 1120, 1000 cm^{-1}; CI-MS (NH_3): 688 $(M + NH_4)^+$ $(C_{35}H_{46}O_{11}Si + NH_4)^+$ (100); ^1H NMR (400 MHz, $CDCl_3$, TMS as reference): δ 7.95 (d, J = 7.6 Hz, Bz), 7.62 (t, J = 7.6 Hz, Bz), 7.48 (t, J = 7.6 Hz, Bz), 5.85 (br d, J = 3.5 Hz, H-10), 5.75 (d, J = 1 Hz, H-2), 5.14 (dd, J = 9.0, 2.0 Hz, H-5), 4.87 (d, J = 8.6 Hz, H-20a), 4.75 (d, J = 8.6 Hz, H-20b), 4.63 (dd, J = 9.9, 7.4 Hz, H-7), 4.50 (d, J = 3.5 Hz, 10-OH), 4.40 (s, 14-OH), 3.59 (br s, H-3), 2.69 (ddd, J = 14.0, 9.0, 7.4 Hz, H-6α), 2.19 (br s, H-18), 1.97 (ddd, J = 14.0, 9.9, 2.0 Hz, H.6β), 1.93 (s, OAc), 1.62 (s, H-19), 1.49 (s, H-16), 1.33 (s, H-17), 0.95 (m, TES), 0.60 (m, TES). ^{13}C NMR (100 MHz, $CDCl_3$, TMS as reference): δ 207.7 (s, C-9), 200.3 (s, C-1), 199.1 (s, C-13), 173.3 (s, C-11), 170.3 (s, OAc), 165.4 (s, Bz), 140.6 (s, C-12), 134.0 (d, Bz), 129.9 (d, Bz), 128.7 (d, Bz), 128.4 (s, Bz), 98.2 (s, C-14), 83.1 (d, C-5), 81.0 (s, C-4), 77.8 (t, C-20), 76.4 (d, C-2), 74.6 (d, C-10), 72.7 (d, C-7), 62.2 (s, C-8), 50.4 (s, C-15), 45.2 (d, C-3), 38.1 (t, C-6), 37.2 (q, C-17), 21.1 (q, OAc), 17.6 (q, C-16), 10.9 (q, C-18), 10.6 (q, C-19), 6.7 (q, TES), 5.3 (t, TES). [^1H- and ^{13}C signals were assigned with the aid of NOEs-inspection and the analysis of the HMBC spectra]
5. **1c** could be obtained in quantitative yield treating **1a** with $Pb(OAc)_4$ (6 mol. equiv., C_6H_6, Δ, 1h).
6. The planar representation of **2a-c** was done according to the Lythgoe convention, that is, the substituent at the bridgehead carbon (C-14) was considered as a ring-B substituent (Eyre, D.H.; Harrison, J.W.; Lythgoe, B. *J. Chem. Soc. (C)* **1967**, 452-462). As customary with taxanes, a normal- and not a dotted line was then used for the bond joining the bridgehead carbon (C-14) to the adjacent carbon of ring-A (C-13).

7. Pretsch, E.; Seibl, J.; Simon, W.; Clerc, T. *Spectral Data for Structure Determination of Organic Compounds*; Springer-Verlag, 1989, C190.
8. Values of 7-8 Hz for $J_{2,3}$ and 40-45 ppm for the chemical shift of C-15 are typical for baccatin III derivatives (Kingston, D.G.I.; Molinero, A.A.; Rimoldi, J.M. *Prog. Chem. Org. Nat. Prod.* **1993**, *61*, 1-192).
9. Kurono, M.; Nakadaira, Y.; Onuma, S.: Sasaki, K.; Nakanishi, K.; *Tetrahedron Lett.* **1963**, 2143-2161.
10. Dukes, M.; Eyre, D.H.; Harison, J.W.; Scrowston, R.M.; Lythgoe, B. *J.Chem. Soc.(C)* **1967**, 448-452.
11. The unambiguous assignment of the carbonyls was based on the detection of a long-range correlations between H-18/C-13, H-19/C-9 and H-2/C-1.
12. To a soln. of **2a** (200 mg) in isopropanol (5 ml), $NaBH_4$ (50 mg) was added. After stirring 5 min. at room temp., the reaction was quenched by the addition of sat. NH_4Cl and worked up by extraction with CH_2Cl_2. The reaction mixture was purified by CC (silica gel, hexane-EtOAc 8:2 as eluant) to give 140 mg **2b**. ^1H NMR (400 MHz, $CDCl_3$, TMS as reference): δ 7.95 (d, J = 7.6 Hz, Bz), 7.62 (t, J = 7.6 Hz, Bz), 7.47 (t, J = 7.6 Hz, Bz), 5.66 (dd, J = 2.5, 1.5 Hz, H-2), 5.73 (d, J = 4.0 Hz, H-10), 5.09 (dd, J = 9.5, 2.0 Hz, H-5), 4.62 (dd, J = 10.0 Hz, 7.5 Hz, H-7), 4.57 (br d, J = 9.0 Hz, H-20a), 4.52 (br d, J = 9.0 Hz, H-20b), 4.44 (d, J = 4.0 Hz, 10-OH), 3.86 (d, J = 2.5 Hz, H-1), 3.73 (br s, 14-OH), 3.47 (br s, H-3), 2.65 (ddd, J = 14.5, 9.5, 7.5 Hz, H-6α), 2.44 (br s, 1-OH), 2.16 (s, H-18), 2.10 (s, OAc), 1.91 (ddd, J= 14.5, 10.0, 2.0 Hz, H-6β). 1.57 (s, H-19), 1.39 (s, H-16), 1.15 (s, H-17), 0.93 (t, J = 7.0 Hz, TES), 0.67 - 0.50 (m, TES). ^{13}C-NMR (100 MHz, $CDCl_3$, TMS as reference): δ 208.3 (s, C-9), 205.2 (s, C-13), 171.5 (s, OAc), 170.6 (s, C-11), 164.4 (s, Bz), 137.4 (s, C-12), 134.0 (d, Bz), 129.8 (d, Bz), 128.8 (d, Bz), 128.6 (s, Bz), 90.1 (s, C.14), 83.9 (d, C-5), 81.8 (d, C-1), 80.6 (s, C-4), 78.1 (t, C-20), 50.1 (s, C-15), 43.1 (d, C-3), 38.1 (t, C-6), 35.7 (q, C-17), 21.8 (q, OAc), 16.8 (q, C-16), 10.8 (q, C-19), 10.1 (q, C-18), 6.7 (q, TES), 5.4 (t, TES). [^1H- and ^{13}C signals were assigned with the aid of NOE-inspection and the HMBC spectra].
13. Paquette, L.A.; Elmore, S.W.; Combrink, K.D.; Hickey, E.R.; Rogers, R.D. *Helv. Chim. Acta* **1992**, *75*, 1755-1771
14. Sato, Y.; Sato, Y.; Kaneko, H.; Bianchi, E.; Kataoka, H. *J. Org. Chem.* **1969**, *34*, 1577-1582.
15. MnO_2 is known to oxidize α-ketols to α-diketones (Fatiadi, A.J.; *Synthesis* **1976**, 65-104).
16. Oil, UV λ_{max} (EtOH):275, 235 nm; IR ν_{max}(liquid film): 3450, 1760, 1730, 1380, 1240, 980, 810, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS as reference): δ 7.96 (d, J = 7.6 Hz, Bz), 7.62 (t, J = 7.6 Hz, Bz), 7.49 (t, J = 7.6 Hz, Bz), 6.81 (s, H-10), 5.82 (br s, H-2), 5.82 (dd, J = 7.1, 3.9 Hz, H-7), 5.18 (br d, J = 7.9 Hz, H-5), 4.95 (d, J = 11.8 Hz, TROC), 4.86 (d, J = 11.7 Hz, TROC), 4.85 (d, J = 8.5 Hz, H-20a), 4.79 (d, J = 11.7 Hz, TROC), 4.77 (d, J = 8.5 Hz, H-20b), 4.60 (d, J = 11.8 Hz, TROC), 3.54 (br s, H-3), 2.90 (m, H-6α), 2.39 (br s, H-18), 2.15 (m, H-6β), 1.96 (s, OAc), 1.58, 1.34, 1.26 (s, H-16, H-17 and H-19). ^{13}C NMR (100 MHz, $CDCl_3$, TMS as reference): δ 199.7, 199.0, 198.8 (s, C-9, C-13 and C-1), 170.3 (s, OAc), 165.4 (s, C-11), 165.2 (s, Bz), 153.8 (s, TROC), 153.0 (s, TROC), 143.4 (s, C-12), 134.1 (d, Bz), 129.9 (d, Bz), 128.8 (d, Bz), 128.2 (s, Bz), 98.7 (s, C-14), 93.9 (s, 2 x TROC), 82.7 (d, C-5), 80.4 (s, C-4), 78.7, 76.5, 75.5 (d, C-2, C-7 and C-10), 77.5 (t, C-20), 77.2 (t, 2 x TROC), 60.2 (s, C-8), 50.6 (s, C-15), 45.4 (d, C-3), 37.0 (q, C-17), 34.2 (t, C-6), 20.9 (q, OAc), 17.3 (q, C-16), 11.6 (q, C-18), 11.2 (q, C-19).
17. Chen, S.H.; Huang, S.; Wei, J.; Farina, V. *Tetrahedron* **1993**, *49*, 2805-2828.
18. Holton, R.A.; Somoza, C.; Chai, K.-B. *Tetrahedron Lett.* **1994**, 1665-1668.

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