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Synthesis of Modified Baccatins *via* an Oxidation-Reduction Protocol[1]

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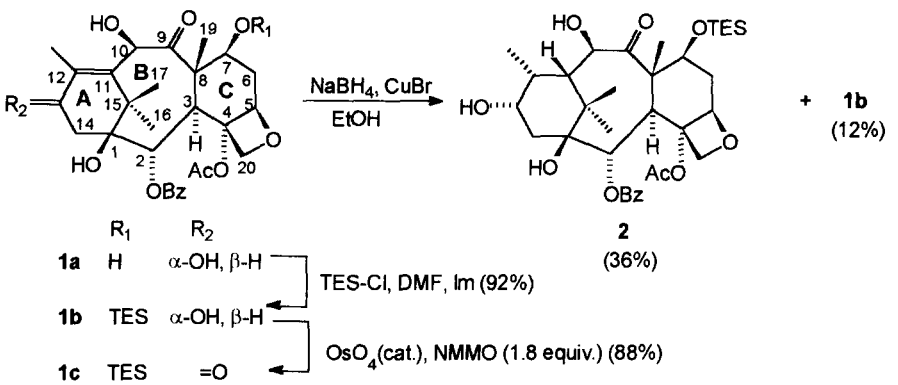
Abstract: *(12R)-7-Trietylsilyl-11-dihydro-10-deacetylbaccatin III* (**2**), *10-epi-10-deacetylbaccatin III* (**4**) *and the 7,8-seco baccatin III* (**5a**) *were synthesized from 10-deacetylbaccatin III* via *an oxidation-reduction protocol.*

The exciting therapeutical profile and the unique mode of activity of the anticancer drug paclitaxel (Taxol®) have fostered studies on the structure-activity relationships within antitumor taxoids.[2] The majority of these investigations have centered on modifications of the acyl residues of the diterpenoid core, and this approach has led to the discovery of a clinically useful analogue [docetaxel (Taxotere®)][3] and of ultrapotent ligands for the taxoid receptor on tubulin.[4] The modification of the heavily functionalized diterpene moiety has been less investigated, also on account of its rather unpredictable reactivity.[5] Epimerization at C-7, deoxygenation at C-7, C-9 and C-10, Wagner-Meerwein rearrangement of the A/B ring system, photocyclization, and oxetane ring opening have been studied, disclosing the importance of certain structural features (e.g. an intact oxetane ring) for a significant anticancer activity.[2] However, several important structural features of the diterpene moiety have not yet been addressed, and a satisfying picture of the structural requirements for antitumor activity is still lacking. Indeed, the inverted-cup shape of the taxane skeleton makes some functional groups unreactive (e.g. the bridgehead double bond) and certain manipulations impossible (e.g. inversion of the C-10 hydroxyl *via* nucleophilic attack from the concave α-face of the molecule). These limitations hold also for 10-deacetylbaccatin III (**1a**), the starting material for the semisynthesis of paclitaxel.[6] We now report that oxidized forms of 10-deacetylbaccatin III undergo reductive processes that make it possible to circumvent some of these restrictions, obtaining diterpenoid precursors of new classes of paclitaxel analogues.

The bridgehead double bond of baccatin III derivatives is totally unreactive toward catalytic hydrogenation and electrophilic attack. Indeed, the benzoyl group at C-2 can be hydrogenated to the corresponding cyclohexanecarboxylate without affecting the double bond of the terpenoid core.[7] However, the introduction of a C-13-keto group makes nucleophilic addition of hydrides to the bridgehead double bond possible, and this process might benefit from the presence of a nearby coordination site (the C-10 β-hydroxyl) to overcome the inherent inaccessibility of the double bond. To test this hypothesis, 7-trietylsilyl(TES)-13-dehydro-10-deacetylbaccatin III (**1c**) was synthesized from 10-deacetylbaccatin III (**1a**) and subjected to borohydride reduction. An almost equimolecular and easily separable mixture of 7-TES-10-deacetylbaccatin III (**1b**)[6] and its

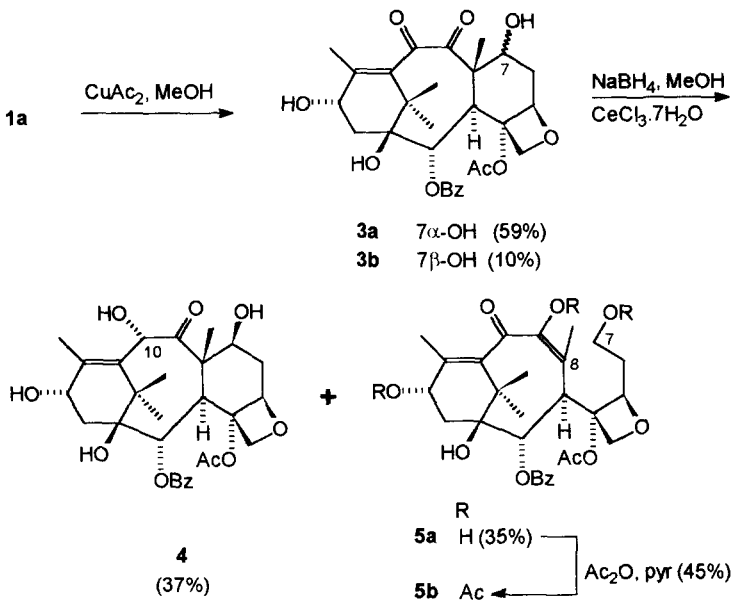
dihydroderivative (**2**)[8] was formed. The α-(*endo*) orientation of the methyl at C-12 and the hydroxyl at C-13 of **2** was established by NOE measurements.[8] Interestingly, the regioselectivity of the reduction was not affected by the presence of lanthanoids,[9] although the ratio between **1b** and **2** was changed by the addition of other inorganic salts. The best results in terms of conjugate reduction were obtained in the presence of CuBr.[9] Under these conditions, the ratio between the mono- and the bireduced products was 1:3.[10] The borohydride reduction of the 10-acetyl derivative of **1c** gave exclusively the product of 1,2-attack (7-TES-baccatin III),[11] showing that boron coordination to the 10-hydroxyl is essential for the conjugate addition.



The C-7 epimerization of taxol and baccatin III derivatives via a retro-aldol mechanism has been known for a long time,[12] but the reductive trapping of the intermediate C-7 aldehyde has never been achieved. We reasoned that the presence of a keto group at C-10 should stabilize the intermediate ring C-cleaved enolate by conjugation, allowing the reductive trapping of the C-7 aldehyde. In the event, treatment of 10-dehydro 10-deacetylbaccatin V (**3a**)[13] or its C-7 epimer **3b** with $NaBH_4$ in methanol gave a complex mixture of products. However, a clean reaction was observed when one molar equivalent of $CeCl_3.7H_2O$ was added, and the same mixture of two crystalline compounds (**4** and **5a**) was obtained from both epimers.[14,15] CI-MS showed the same molecular formula for **4** and **5a** ($C_{29}H_{36}O_{10}$), corresponding to the addition of two hydrogen atoms to **3a,b**.

The NMR spectra of the less polar isomer (**4**)[16] and 10-deacetylbacatin III (**1a**)[17] showed the same spin systems, coupling constants and carbon multiplicities. Changes in the chemical shift of C-10 and the detection of NOE effects between H-10 and the methyls C-16 and C-19 showed that **4** is 10-deacetyl-10-epibaccatin III. The obtaining of only the 7β-hydroxy derivative **4** from the reduction of **3a** and **3b** suggests that in the 10-epibaccatin III series the retroaldol equilibration is shifted toward the equatorial (β) aldol. The major driving force for the equatorial (β)- to axial (α) C-7 epimerization of baccatin III derivatives is the formation of an intramolecular hydrogen bonding between the 7α-hydroxyl and the 4-acetate carbonyl.[12,18] However, in compounds of the 10-epi series, the 4-acetyl is spatially close and hydrogen bonded to the 10α-hydroxyl,[19] and the aldol equilibration is thus mainly affected by steric factors, obviously favoring the equatorial (β) orientation of the 7-hydroxyl. The structure elucidation of the more polar isomer (**5a**) was not straightforward, since this compound showed uninformative NMR spectra over a wide range of temperatures. Indeed, only broad humps could be detected at room temperature, and marked changes with the temperature showed that this compound was a mixture of equilibrating rotamers. Only the averaged spectrum taken at 130° in DMSO-d_6 was amenable to structural analysis.[20] The presence of a pair of diastereotopic H-7 protons (δ 3.52 and 3.41) and the resonance of H-19 as an allylic methyl (δ 1.93, br s) suggested a ring C-seco structure for **5a**. The presence of an enolic hydroxyl was confirmed by the detection of a low-field exchangeable signal (9-OH, δ 6.74 in $CDCl_3$-Me_2CO-d_6) and by the preparation of the enol acetate **5b** (ν C=O 1785 cm^{-1}).[21] **5b** showed conformational features similar to those of **5a**.

The easy synthesis of the modified baccatins **2**,**4** and **5a** illustrates the subtle relationship between structure and reactivity in taxoids and provides the opportunity for the preparation of new analogues of paclitaxel.



REFERENCES AND NOTES

1. Part XXI in the series: The Chemistry and Occurrence of Taxane Derivatives. For part XX, see:Gabetta, B.; De Bellis, P.; Pace, R.; Appendino, G.; Barboni, L.; Gariboldi, P.; Torregiani, E.. *J. Nat. Prod.* (submitted for publication).
2. Hepperle, M.; Georg, G.I. *Drugs Fut.* **1994**, *19*, 573-584.
3. Guénard, D.; Guéritte-Voegelein, F.; Potier, P. *Acc. Chem. Res.* **1993**, *26*, 160-167.
4. Chaudhary, A.G.; Gharpure, M.M.; Rimoldi, J.M.; Chordia, M.D.; Leslie Gunatilaka, A.A.; Kingston, D.G.I.; Grover, S.; Lin, C.M.; Hamel, E. *J. Am. Chem. Soc.* **1994**, *116*, 4097-4098.
5. Appendino, G.; Jakupovic, J.; Cravotto, G.; Varese, M. *Tetrahedron Lett.* **1994**, *35*, 6547-6550.
6. Denis, J.-D.; Greene, A.E.; Guénard, D.; Guéritte-Voegelein, F.; Mangatal, L.; Potier, P.; *J. Am. Chem. Soc.* **1988**, *110*, 5197-5199.
7. a) Samarayake, G.; Neidigh, K.A.; Kingston, D.G.I. *J. Nat. Prod.* **1993**, *56*, 884-898. b) Ojima, I.; Duclos, O.; Zucco, M.; Bissery, M.-C.; Combeau, C.; Vrignaud, P.; Lavelle, F. *J. Med. Chem.* **1994**, *37*, 2602-2608.
8. ^{1}H NMR (400 MHz, $CDCl_3$, TMS as reference): δ 8.16 (d, J=7.6 Hz, Bz), 7.59 (t, J=7.6 Hz, Bz), 7.47 (t, J= 7.6 Hz, Bz), 5.61 (d, J=8.5 Hz, H-2), 5.10 (dd, J=9.5, 2.5 Hz, H-5), 4.96 (dd, J=8.5, 5.0 Hz, H-10), 4.36 (br d, J=8.5 Hz, H-3), 4.33 (d, J=8.0 Hz, H-20a), 4.31 (dd, J=11.5, 6.5 Hz, H-7), . 4.27 (dd, J=8.0, 1.0 Hz, H-20b), 4.03 (ddd, J=6.5, 3.0, 3.0 Hz, H-13), 3.33 (d, J=8.5 Hz, 10-OH), 2.47 (ddd, J=14.0, 9.5, 6.5 Hz, H-6α), 2.45 (br d, J=16.5 Hz, H-14α), 2.36 (m, H-12), 2.24 (s, Ac), 2.11 (dd, J=3.0, 2.0 Hz, 13-OH), 1.85 (ddd, J=14.0, 11.0, 2.5 Hz, H-6β), 1.79 (dd, J=16.5, 6.5 Hz, H-14β), 1.75 (s, 1-OH), 1.75 (br dd, J=5.0, 4.0, H-11),1.70 (s, H-19), 1.23 (d, J=7.0 Hz, H-18), 1.11 (s, H-17), 1.02 (s, H-16), 0.93 (t, J=7.0 Hz, Tes), 0.54 (q, J=7.0 Hz, Tes). Diagnostical NOEs: H-18/H-10, H-18/13-OH,, H-12/H-17, H-12/H-11, H-3/13-OH. ^{13}C NMR (100 MHz, $CDCl_3$, TMS as reference): δ 215.1 (s, C-9), 169.9 (s, Ac), 167.7 (s, Bz), 133.5 (d, Bz), 130.1 (d, Bz), 129.8 (s, Bz), 128.5 (d, Bz), 83.8 (d, C-5), 80.1 (s, C-4), 79.8 (s, C-1), 76.5 (t, C-20), 73.4 (d, C-2), 71.6 (d, C-7), 70.9 (d, C-13), 69.4 (d, C-10), 60.6 (d. C-11), 56.4 (s, C-8), 40.6 (d, C-3), 40.3 (s, C-15), 36.4 (t, C-6), 35.4 (t, C-14), 32.5 (d, C-12), 32.5 (q, C-17), 25.6

(q, C-16), 22.3 (q, Ac), 15.6 (q, C-18), 9.1 (q, C-19), 6.8 (q, Tes), 5.3 (t, Tes). The ^{1}H- and ^{13}C NMR spectra of **2a**, and **4** were assigned with the aid of NOE-inspection and the HMBC spectra.

9. Gemal, A.L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454-5459.
10. To a solution of **1c** (1.0 g, 1.52 mmol) in EtOH, CuBr (1 mol. equiv.) was added. After stirring 15 min. at room temp., an excess $NaBH_4$ (400 mg, 10.6 mmol) was added. After 30 min. the reaction was worked up by the addition of sat. NH_4Cl and extracted with $CHCl_3$. Evaporation of the organic phase gave a residue that was purified by CC (hexane-EtOAc 8:2 as eluant) to give 361 mg **2** (36%) and 120 mg **1b** (12%).
11. Nicolaou, K.,C.; Yang, Z.; Liu, J.J.; Ueno, H.; Nantermet, P.G.; Guy, R.K.; Claiborne, C.F.; Renaud, J.; Couladouros, E.A.; Paulvannan, K.; Sorensen, E.J. *Nature* **1994**, *367*, 630-634.
12. a) Miller, R.W.; Powell, R.G.; Smith Jr., C.R.; Arnold, E.; Clardy, J. *J. Org. Chem.* **1981**, *46*, 1469-1474. b) McLaughlin, J.L.; Miller, R.W.; Powell, R.G.; Smith Jr., C.R. *J. Nat. Prod.* **1981**, *44*, 312-319.
13. Appendino, G.; Fenoglio, I.; Cravotto, G.; Varese, M.; Gariboldi, P.; Gabetta, B. *Gazz. Chim. Ital.* **1994**, *124*, 253-257.
14. The hard acid Ce^{3+} might stabilize the α-ketoenolate by coordination, or shut down the conjugate reduction of the C-11 double bond.
15. To a solution of **3a** (500 mg) in methanol (50 ml), $CeCl_3.7H_2O$ (1 mol. equiv.) was added. After stirring at room temp. for 5 min., an excess $NaBH_4$ (250 mg) was added. After 20 min. the reaction was worked up by the addition of sat. NH_4Cl and extracted with EtOAc. Evaporation of the organic phase gave a residue that was purified by CC (silica gel, hexane-EtOAc 1:9 as eluant) to give 185 mg **4** (37%) and 175 mg **5a** (35%).
16. ^{1}H NMR (300 MHz, $CDCl_3$, TMS as reference): δ 8.12 (d, J=7.6 Hz, Bz), 7.58 (t, J=7.6 Hz, Bz), 7.49 (t, J=7.6 Hz, Bz), 5.68 (d, J=6.8 Hz, H-2), 5.20 (br s, H-10), 5.03 (d, J=8.1 Hz, H-5), 4.76 (m, H-13 and H-7), 4.33 (d, J=8.3 Hz, H-20a), 4.26 (d, J=6.8 Hz, H-3), 4.18 (d, J=8.3 Hz, H-20b), 2.52 (m, H-6α), 2.31 (s, Ac), 2.18 (s, H-18), *ca* 2.10 (m, H-14α,β), 1.90 (m, H-6β),1.69 (s, H-19), 1.15 (s, H-16), 1.13 (s, H-17). ^{13}C NMR (75 MHz, DMSO-d_6, TMS as reference): δ 208.4 (s, C-9), 169.7 (s, Ac), 165.7 (s, Bz), 135.5 (s, C-12), 133.,6 (d, Bz), 131.3 (s, C-11), 130.7 (s, Bz), 129.9 (d, Bz), 129.1 (d, Bz), 84.2 (d, C-5), 82.0 (d, C-10), 80.3 (s. C-4), 77.1 (s, C-1), 76.1 (t, C-20), 75.6 (d, C-2), 69.9 (d, C-7), 66.7 (d, C-13), 60.0 (s, C-8), 45.2 (d, C-3), 43.0 (s, C-15), 39.3 (t, C-14), 36.3 (t, C-6), 26.8 (q, C-17), 22.7 (q, Ac), 22.5 (q, C-16), 14.0 (q, C-18), 11.0 (q, C-19).
17. Appendino, G.; Gariboldi, P.; Gabetta, B.; Pace, R.; Bombardelli, E.; Viterbo, D.; *J. Chem. Soc., Perkin Trans. 1* **1992**, 2925-2929.
18. Castellano, E.E.; Hodder, O.J.R. *Acta Cryst.* **1973**, *B29*, 2566-2570.
19. This intramolecular hydrogen bonding is probably responsible for the remarkable differences in polarity between **1a** and **4**. Indeed, the chromatographic behavior and solubility of **4** are similar to those of the 7-epimer of **1a**, where the 4-acetyl is hydrogen bonded to the 7α-hydroxyl.
20. ^{1}H NMR (400 MHz, DMSO-d_6, TMS as reference, 130°C): δ 8.02 (d, J=7.6 Hz, Bz), 7.62 (t, J=7.6 Hz, Bz), 7.51 (t, J=7.6 Hz, Bz), 5.49 (d, J=9.0 Hz, H-2), 5.04 (dd, J=11.0, 2.5 Hz, H-5), 4.80 (br dd, J=9.0, 6.5 Hz, H-13), 4.74 (d, J=8.0 Hz, H-20a), 4.39 (d, J=9.0 Hz, H-3), 4.16 (d, J=8.0 Hz, H-20b),3.52 (ddd, J=10.0, 6.5, 5.0 Hz, H-7a), 3.41 (ddd, J=10.0, 8.0, 5.0 Hz, H-7b), 2.56 (dd, J=16.0, 6.5 Hz, H-14a), 2,32 (dd, J=16.0, 9.0 Hz, H-14b), 2.25 (dddd, J=14.5, 8.0, 6.5, 2.5 Hz, H-6a), 1.97 (s, Ac), 1.93 (s, H-19), 1.91 (m, H-6'), 1.85 (d, J=1.5 Hz, H-18), 1.10 (s, H-17), 1.05 (s, H-16). Owing to severe line-broadening, only few ^{13}C-NMR resonances of the diterpene moiety could be detected. Among those diagnostical of structure **5a**, C-10 (δ 192.2, s) and C-9 (δ 165,1, s) could be observed, but the signals of C-7 and C-8 were broadened beyond detection. Based on the presence of correlation peaks in the H,C-COSY (H-7a,b/C-7) and HMBC spectra (H-2/C-8), these carbons should resonate around 59 ppm (C-7) and 122 ppm (C-8).
21. ^{1}H-NMR (400 MHz, $CDCl_3$, TMS as reference, 60°C): δ 8.00 (d, J=7.6 Hz, Bz), 7.63 (t, J=7.6 Hz, Bz), 7.50 (t, J=7.6 Hz, Bz), 6.11 (br t, J=8.0 Hz, H-13), 5.66 (d, J=8.0 Hz, H-2), 5.21 (br m, H-5), 5.03 (d, J=8.2 Hz, H-20a), 4.57 (br d, J=8.0 Hz, H-3), 4.38 (br d, J=8.2 Hz, H-20b), 4.33 (m, H-7a), 4.11 (td, J=10.0, 4.0 Hz, H-7b), 2.57 (m, H-14a), 2.48 (m, H-6a), 2.45 (m, H-14b), 2.28 (s, Ac), 2.22 (s, Ac), 2.02 (s, Ac), 2.10 (m, H-6b), 1.95 (s, H-19), 1.87 (s, H-18), 1.26 and 1.20 (s, H-16 and H-17).

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