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14β-Hydroxy-10-deacetylbaccatin III as a convenient, alternative substrate for the improved synthesis of methoxylated second-generation taxanes

Luciano Barboni,[a,*] Guido Giarlo,[a] Roberto Ballini[a] and Gabriele Fontana[b]

[a]*Dipartimento di Scienze Chimiche, Università di Camerino, Via S. Agostino 1, 62032 Camerino (MC), Italy*
[b]*Indena S.p.A. Viale Ortles 12, 20139 Milano, Italy*

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Abstract—This article describes a new, convenient, improved synthesis of the 2-debenzoyl-2-*m*-methoxybenzoyl-7-triethylsilyl-13-oxo-14β-hydroxybaccatin III 1,14-carbonate, the key intermediate in the synthesis of two new second-generation antitumor taxanes.

The antimitotic drugs Taxol® (paclitaxel) and Taxotere® (docetaxel) are two of the best anticancer agents in clinical use today for the treatment of ovarian cancer, breast cancer, and nonsmall cell lung cancer. Paclitaxel and docetaxel suffer from a series of disadvantages, including poor water solubility and the quick development of resistance,[1] that have fuelled the search for analogues endowed with a better clinical profile.

In this context, we recently published the synthesis of two new biologically active compounds (**1** and **2**, Fig. 1),[2] the methoxylated analogues of the norstatin esters IDN5109 and IDN5390 (**3** and **4**, respectively; Fig. 1)[3] which have recently emerged as interesting clinical candidates to overcome resistance to paclitaxel and to allow oral administration.

The synthesis of both compounds **1** and **2** was accomplished starting from the naturally occurring 10-deacetylbaccatin III **5** (Scheme 1), through the key intermediate **6**.

The synthesis of **6** from **5** proceeded in an unsatisfactory overall yield (7%), due to the presence of two critical steps. In fact, since 10-deacetylbaccatin III lacks the β-oxygen at C-14, the procedure required the diastereoselective β-hydroxylation, followed by carbonylation of the crude 1,14-diol,[4] with a low overall yield (30%). This prompted us to explore an alternative synthesis for the key compound **6**, with the aim of avoiding the diastereoselective hydroxylation step and, in this way, to increase the yield of the synthesis. The new approach started from the readily available 14β-hydroxy-10-deacetylbaccatin III (**7**), a naturally occurring taxane isolated from

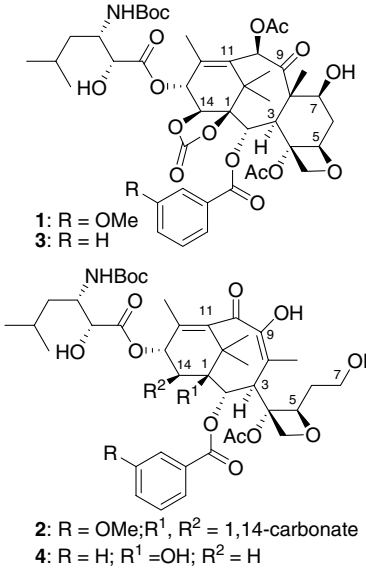

Figure 1.

Keywords: 14β-Hydroxy-10-deacetylbaccatin III; Second-generation taxanes; Natural products; Terpenoids; Antitumor agents.
* Corresponding author. Tel.: +39 0737402240; fax: +39 0737637345; e-mail: luciano.barboni@unicam.it

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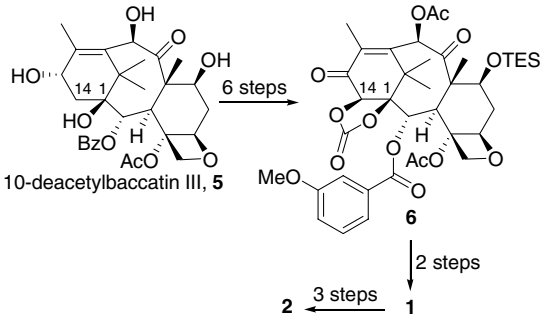


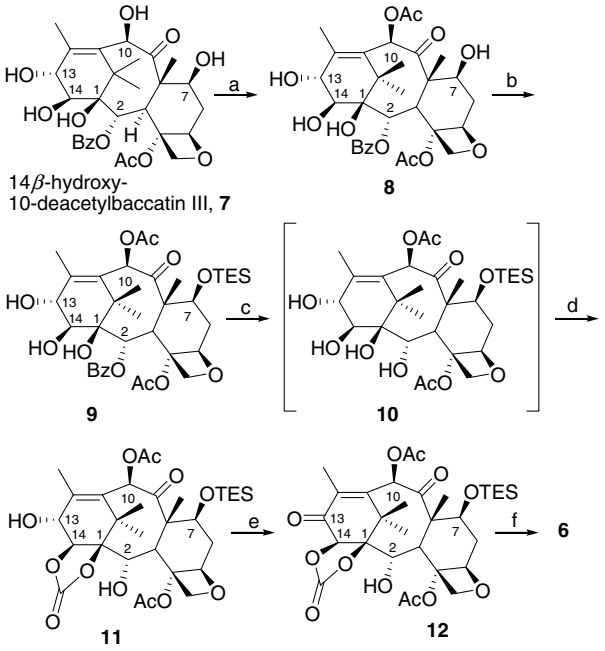
Scheme 1. Synthesis of **1** and **2** from 10-deacetylbaccatin III (**5**); see Ref. 2.

Taxus wallichiana Zucc.[5] which, compared to 10-deacetylbaccatin III, shows an additional β-hydroxyl group at C-14.

The first step of our procedure was the selective acetylation of the 10-hydroxyl group, which was carried out by treatment with Ac_2O in the presence of $CeCl_3{\cdot}7H_2O$,[6] which gave compound **8** with a 98% yield, followed by the selective silylation of the 7-hydroxyl group[7] (Scheme 2) to give **9** (55%). The obtained compound **9** was then debenzoylated at C-2 by treatment with benzyltrimethylammonium hydroxide (Triton B)[8] giving the polyhydroxylated compound **10**. The crude **10** was then selectively carbonylated at 1,14 with triphosgene[9] to yield compound **11** (56% from **9**). The latter was selectively oxidized at C-13 by treating with *N*-methylmorpholine-*N*-oxide and a catalytic amount of OsO_4,[10] to yield ketone **12** (93%, Scheme 2). Finally, **12** was benzoylated at C-2 with anisic acid,[11] allowing the target compound **6** to be obtained in an acceptable yield of 40% (Scheme 2).[12] It is worth noting that, as far as we know, the benzoylation at C-2 of a taxane, in the presence of the 1,14-carbonate, has never been reported before. The limited yield of this step is probably due to the steric hindrance that the 1,14-carbonate and the 4-acetate are exerting on the C-2 hydroxyl group.

The overall yield of the synthesis was 11%, which represents a significant increase (>50%) compared to 7% of the previous procedure. Additionally, the chance to have two approaches for the synthesis of highly active antitumor taxanes, from different naturally occurring compounds, could be very useful since the restricted availability of the starting material is, usually, one of the main limiting factor.[13]

In summary, a convenient preparation of the key intermediate **6** has been reported; the method includes the first benzoylation at C-2 of a taxane carrying a 1,14 carbonate. This synthetic procedure starts from a different precursor and involves simpler chemistry compared with those from 10-deacetylbaccatin III. Moreover, a substantial increase of the yield (>50%) with respect to the previous procedure is the crucial advantage of this method. Further studies on the synthesis of antitumor taxanes are in progress.



Scheme 2. Synthesis of **6** from 14β-hydroxy-10-deacetylbaccatin III (**7**). Reagents and conditions: (a) Ac_2O, $CeCl_3{\cdot}7H_2O$, THF, overnight, 98%; (b) TESCl, pyridine, overnight, 55%; (c) Triton B, DCM, −78 °C → 0 °C, 1.5 h; (d) triphosgene, pyridine, DCM, 0 °C, 10 min, 56%; (e) *N*-methylmorpholine-*N*-oxide, OsO_4, acetone, 0 °C → rt, 1 h, 93%; (f) anisic acid, DCC, DMAP, toluene, 60 °C, 2.5 h, 40%.

Acknowledgments

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12. Experimental procedures for the synthesis of compounds **11**, **12** and **6**. Compound **11**: to a CH_2Cl_2 (25 ml) solution of **9** (71 mg, 1 mmol), cooled at −78 °C, Triton B (0.91 ml, 2 mmol) was slowly added and the temperature was left to rise to 0 °C. After 1.5 h, HCl 5% (40 ml) was added and the mixture was extracted with CH_2Cl_2 (40 ml). The organic layer was washed with $NaHCO_3$ 5% (20 ml), H_2O (20 ml), and brine (20 ml), and then dried over Na_2SO_4 and the solvent was evaporated. The crude compound **10** was dissolved in CH_2Cl_2 (70 ml) and cooled to 0 °C under N_2 atmosphere. Pyridine (1.6 ml, 20 mmol) and triphosgene (297 mg, 1 mmol) were then added. After 5 min, a saturated solution of NH_4Cl (90 ml) was added. The organic layer was diluted with EtOAc (40 ml), washed with H_2O (20 ml) and brine (20 ml), dried over Na_2SO_4, and the solvent evaporated. Purification by column chromatography (hexane/EtOAc 1:1) afforded compound **11** (357 mg, 56% from **9**). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.52 (m, 6 H), 0.87 (t, J = 7.6 Hz, 9H), 1.11 (s, 6H), 1.59 (s, 3H), 1.82 (m, 1H), 2.08 (s, 3H), 2.12 (s, 3H), 2.16 (s, 3H), 2.46 (m, 1H), 3.33 (d, J = 7.1 Hz, 1H), 4.24 (d, J = 7.1 Hz, 1H), 4.41 (dd, J = 10.6, 6.5 Hz, 1H), 4.52 (d, J = 9.0 Hz, 1H), 4.57 (d, J = 9.0 Hz, 1H), 4.60 (d, J = 5.6 Hz, 1H), 4.86 (br d, J = 5.6 Hz, 1H), 4.90 (br d, J = 9.8 Hz, 1H), 6.34 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 5.3, 6.8, 10.5, 14.9, 20.9, 21.7, 22.5, 26.2, 37.1, 41.2, 47.5, 58.6, 68.6, 71.5, 72.2, 75.4, 77.8, 81.2, 83.8, 84.3, 90.0, 132.2, 143.2, 154.5, 169.1, 170.7, 202.2; MS (ESI) *m*/*z* 661 ($M+Na^+$). Compound **12**: to a dry acetone solution (1 ml) of *N*-methylmorpholine-*N*-oxide (293 mg, 2.5 mmol), cooled at 0 °C under N_2, OsO_4 (0.2 M in toluene, 0.5 ml, 0.1 mmol) was added. After stirring for 10 min, compound **11** (1 mmol) was added, dissolved in dry acetone (12 ml). After 30 min at 0 °C, the temperature was left to rise to rt and, after stirring for further 30 min, sodium *m*-bisulfite (1.9 g, 10 mmol) was added. After 1 h, the reaction mixture was diluted with H_2O (20 ml), extracted with $CHCl_3$ (3 × 10 ml), dried over Na_2SO_4, and the solvent evaporated, giving compound **12** (613, 93%). ^{1}H NMR ($CDCl_3$, 200 MHz):δ 0.59 (m, 6H), 0.94 (t, J = 7.57 Hz, 9H), 1.19 (s, 3H), 1.22 (s, 3H), 1.66 (s, 3H), 1.91 (m, 1H), 2.05 (s, 3H), 2.19 (s, 3H), 2.21 (s, 3H), 2.52 (m, 1H), 3.51 (d, J = 6.7 Hz, 1H), 4.41 (d, J = 6.7 Hz, 1H), 4.45 (dd, J = 10.7, 6.5 Hz, 1H), 4.61 (br s, 2H), 4.67 (s, 1H), 4.90 (br d, J = 9.9 Hz, 1H), 6.46 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 5.5, 6.9, 10.3, 14.1, 19.3, 20.9, 21.9, 33.1, 37.2, 41.8, 46.0, 59.3, 68.8, 72.3, 74.9, 77.0, 77.7, 81.2, 83.9, 87.9, 139.4, 151.3, 152.5, 168.9, 170.6, 191.7, 200.0; MS (ESI) *m*/*z* 659 ($M+Na^+$). Compound **6**: to a dry CH_2Cl_2 (30 ml) solution of **12** (637 mg, 1 mmol), anisic acid (1.8 g, 12 mmol), DCC (2.5 g, 12 mmol), and DMAP (1.5 g, 12 mmol) were added, and the temperature was raised to 60 °C for 4 h. 10 ml of EtOH was then added and, after stirring overnight, the mixture was diluted with EtOAc (100 ml) and filtered through Celite and silica gel. Finally, solvent evaporation and chromatography (hexane/EtOAc 7:3) gave compound **6** (308, 40%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.56 (q, J = 7.8 Hz, 6H), 0.90 (t, J = 7.8 Hz, 9H), 1.16 (s, 3H), 1.34 (s, 3H), 1.70 (s, 3H), 1.89 (m, 1H), 2.17 (s, 3H), 2.21 (s, 6H), 2.52 (m, 1H), 3.77 (d, J = 6.9 Hz, 1H), 3.83 (s, 3H), 4.18 (d, J = 8.7 Hz, 1H), 4.35 (d, J = 8.7 Hz, 1H), 4.44 (m, 1H), 4.75 (s, 1H), 4.89 (br d, J = 7.8 Hz, 1H), 6.08 (d, J = 6.9 Hz, 1H), 6.49 (s, 1H), 7.14 (br d, J = 8.7 Hz, 1H), 7.37 (t, J = 8.0 Hz, 1H), 7.49 (br s, 1H), 7.54 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 5.2, 6.7, 9.8, 13.9, 19.3, 20.7, 21.7, 32.7, 36.9, 41.6, 45.4, 55.4, 59.2, 68.3, 72.0, 74.6, 75.8, 77.1, 80.5, 83.8, 86.4, 114.7, 120.7, 122.0, 128.9, 130.0, 139.3, 151.1, 151.3, 159.8, 164.3, 168.7, 170.2, 190.8, 199.0; MS (ESI) *m*/*z* 793 ($M+Na^+$).
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