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Rearrangement of the major taxane from *Taxus canadensis*

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Abstract

The rearrangement of 9-dihydro-13-acetylbaccatin III, the major taxane from *Taxus canadensis*, has been studied. Two new cyclization products as well as one novel degradation compound are reported. Their structures were determined by spectroscopic techniques.

Keywords: taxoids; rearrangements; basicity; sodium methoxide.

The efficacy of the natural product Taxol® against various cancers,[1] its unique mode of action,[2] and its unusual diterpene structure combined with unexpected chemistry[3] triggered an intensive research effort from the international community. Taxanes of the same structural family as Taxol® were isolated from different yews and characterized. *Taxus canadensis*, a low trailing shrub very common in Quebec, is much more widespread than the *Taxus brevifolia*[4] from which Taxol® was originally isolated. The Canadian yew is also an interesting plant since its composition of taxanes differs from other yews. Indeed, it is the only species which produces in its needles a major taxane, 9-dihydro-13-acetylbaccatin III (**1**) which is at least five times more abundant then paclitaxel.[5–7] Acidic rearrangement of **1** led to new *abeo*-taxanes.[8–10] Treatment of other taxane compounds with base led to novel rearrangements.[11,12] In this report we wanted to investigate if it was possible to open ring A of taxane **1** while keeping ring C intact.

As a starting material, we used the acetonide **2** in order to prevent base attack on the hydroxyls at C-7 or C-9. It was prepared from dimethoxypropane and *p*-TSA in acetone following reported procedure.[8,13] In addition, a ketone on C-13 was essential to induce the cleavage of ring A. The C-13 acetyl can be removed by alkyllithium following the procedure of Klein et al. with a yield of ~50%.[13] We found that it was possible to deacetylate C-13 using sodium borohydride in THF:0.05 M potassium phosphate, pH=7.0 buffer (2:1). This method had only been used to cleave the C-13 side chain of paclitaxel.[14] The advantage of this procedure is that the reaction is done at room temperature instead of –40°C or –80°C which are

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the conditions used with methyllithium or butyllithium. In addition, alkyllithiums decompose readily with time whereas $NaBH_4$ is a stable solid. If we use sequential addition of the hydride reagent over a seven hour period (three additions of five equivalents) the yield of taxane **3** is similar to the alkyllithium reaction,[13] even slightly higher (60%). If the reaction proceeds for 24 h with multiple additions of the hydride reagent, the yield of the desired taxane **3** decreases (41% yield) with the formation of an acetonide between C-13 and C-9 hydroxyls: taxane **4** (28% yield).† Taxane **3** was oxidized with Jones reagent and after work up, the resulting enone 5‡ (85% yield) was treated overnight at 4°C with sodium methoxide in methanol. This reaction resulted in a debenzoylation at C-2 and formation of an acetonide between the C-9 and C-2 hydroxyls giving taxane **6** (80% yield). Further reactions with sodium methoxide in methanol for two additional overnight runs led to a degradation product: taxane **7** (10% yield). Taxanes **6** and **7** were characterized by NMR spectroscopy and high resolution mass spectrometry confirmed the elemental composition of the sodiated quasimolecular ions of **6**§ and **7**.¶ A possible mechanism of the

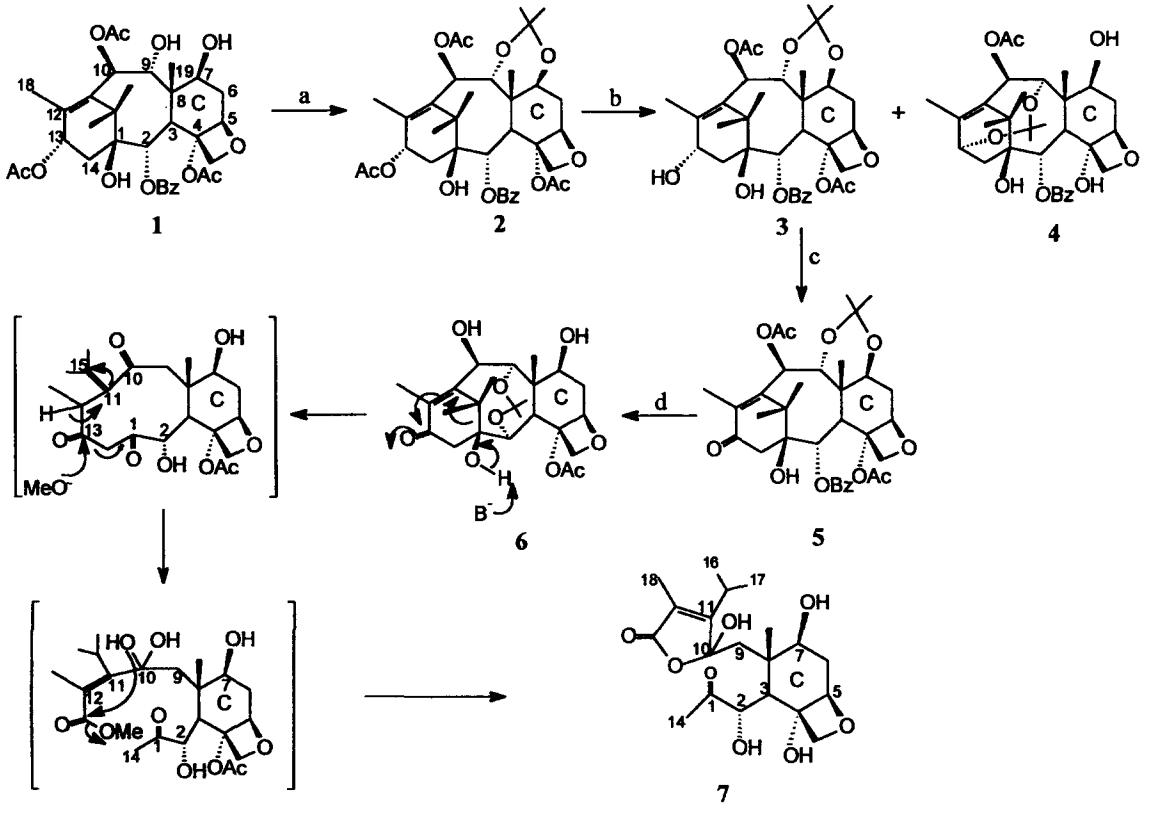
† Taxane **4**: HRFABMS *m/z* 609.2673 ($M+Na^+$), calculated for $C_{32}H_{42}O_{10}Na$, 609.2676; ^1H NMR δ (ppm) 8.07 (2H, d, J=7.6 Hz, H-2,6 of OBz), 7.59 (1H, t, J=7.6 Hz, H-4 of OBz), 7.46 (2H, t, J=7.6 Hz, H-3,5 of OBz), 6.43 (1H, d, J=10.7 Hz, H-10), 5.80 (1H, d, J=4.4 Hz, H-2), 4.65 (1H, dd, J=9.5, 4.9 Hz, H-5), 4.53 (1H, br.d, J=10.0 Hz, H-13), 4.48 (1H, d, J=8.8 Hz, H-20a), 4.46 (1H, d, J=11.2 Hz, H-9), 4.14 (1H, d, J=8.6 Hz, H-20b), 3.90 (1H, dd, J=10.7, 6.3 Hz, H-7), 2.96 (1H, d, J=4.9 Hz, H-3), 2.65 (1H, br.d, J=15.9 Hz, H-14a), 2.42 (1H, dd, J=15.4, 10.3 Hz, H-14b), 2.36 (1H, ddd, J=15.6, 9.3, 6.6 Hz, H-6a), 2.19 (3H, s, H-18), 2.15 (3H, s, OAc), 1.96 (1H, ddd, J=15.4, 11.0, 4.9 Hz, H-6b), 1.62 (3H, o.s, H-19), 1.52 (3H, s, H-17), 1.50 (3H, s, methyl of acetonide), 1.46 (3H, s, methyl of acetonide), 0.99 (3H, s, H-16); ^{13}C NMR δ (ppm) 170.2 (CO-OAc), 166.7 (CO-OBz), 142.3 (C-12), 135.9 (C-11), 133.7 (C-4 of OBz), 130.0 (C-2,6 of OBz), 129.3 (C-1 of OBz), 128.7 (C-3,5 of OBz), 97.8 (C-acetonide), 87.5 (C-5), 80.9 (C-20), 78.4 (C-9), 76.9 (C-4), 76.9 (C-1), 73.7 (C-10), 73.0 (C-2), 69.0 (C-13), 67.8 (C-7), 47.4 (C-3), 41.4 (C-15), 40.4 (C-8), 37.8 (C-14), 34.6 (C-6), 31.5 (C-methyl of acetonide), 29.9 (C-16), 24.8 (C-methyl of acetonide), 21.3 (OAc), 19.9 (C-17), 16.5 (C-18), 14.2 (C-19).

‡ Taxane **5**: HRFABMS *m/z* 627.2804 ($M+H^+$), calculated for $C_{34}H_{42}O_{11}+H^+$, 627.2805; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.07 (2H, d, J=7.8 Hz, H-2,6 of OBz), 7.62 (1H, t, J=7.4 Hz, H-4 of OBz), 7.49 (2H, t, J=7.8 Hz, H-3,5 of OBz), 6.55 (1H, d, J=10.6 Hz, H-10), 5.92 (1H, d, J=6.0 Hz, H-2), 4.84 (1H, d, J=8.9 Hz, H-5), 4.54 (1H, d, J=10.6 Hz, H-9), 4.32 (1H, d, J=8.4 Hz, H-20a), 4.20 (1H, o.t, J=8.6 Hz, H-7), 4.17 (1H, o.d, J=8.8 Hz, H-20b), 3.23 (1H, d, J=5.8 Hz, H-3), 2.91 (1H, d, J=19.6 Hz, H-14a), 2.62 (1H, d, J=19.6 Hz, H-14b), 2.48 (1H, ddd, J=15.4, 7.0, 1.5 Hz, H-6a), 2.19 (3H, s, H-18), 2.17 (3H, s, OAc), 2.15 (3H, s, OAc), 1.78 (1H, m, H-6b), 1.74 (3H, s, H-19), 1.60 (3H, s, H-17), 1.51 (3H, s, methyl of acetonide), 1.46 (3H, s, methyl of acetonide), 1.16 (3H, s, H-16); ^{13}C NMR ($CDCl_3$, HMQC data) 198.2 (C-13), 170.0 (CO-OAc), 169.7 (CO-OAc), 167.0 (CO-OBz), 153.6 (C-12), 139.9 (C-11), 134.0 (C-4 of OBz), 130.1 (C-2,6 of OBz), 128.9 (C-1 of OBz), 128.8 (C-3,5 of OBz), 97.9 (C-acetonide), 83.6 (C-5), 81.4 (C-4), 78.2 (C-1), 78.1 (C-9), 76.6 (C-20), 74.1 (C-10), 72.5 (C-2), 68.2 (C-7), 43.5 (C-3), 42.7 (C-14), 42.6 (C-8), 41.0 (C-15), 34.5 (C-6), 33.6 (C-16), 31.5 (C-methyl of acetonide), 24.7 (C-methyl of acetonide), 21.8 (OAc), 21.1 (OAc), 19.7 (C-17), 14.2 (C-19), 13.4 (C-18).

§ Taxane **6**: HRFABMS *m/z* 503.2258 ($M+Na^+$), calculated for $C_{25}H_{36}O_9Na$, 503.2257; ^1H NMR δ (ppm) 5.39 (1H, d, J=10.3 Hz, H-10), 4.85 (1H, d, J=8.6 Hz, H-20a), 4.63 (1H, dd, J=9.2, 3.7 Hz, H-5), 4.34 (1H, d, J=8.5 Hz, H-20b), 4.25 (1H, d, J=10.5 Hz, H-9), 4.11 (1H, o.m, H-2), 3.79 (1H, dd, J=10.5, 7.1 Hz, H-7), 3.02 (1H, d, J=19.3 Hz, H-14a), 2.84 (1H, s, OH-10), 2.58 (1H, d, J=19.3 Hz, H-14b), 2.37 (1H, o.ddd, J=15.6, 9.3, 6.9 Hz, H-6a), 2.16 (1H, o.m, H-3), 2.04 (3H, s, OAc), 1.96 (3H, o.s, H-18), 1.95 (1H, o.m, H-6b), 1.63 (3H, o.s, H-19), 1.61 (3H, s, methyl of acetonide), 1.53 (3H, s, H-17), 1.50 (3H, s, methyl of acetonide), 1.32 (3H, s, H-16); ^{13}C NMR δ (ppm) 199.5 (C-13), 170.0 (CO-OAc), 156.8 (C-11), 137.7 (C-12), 98.1 (C-acetonide), 84.9 (C-5), 82.2 (C-20), 81.4 (C-9), 77.8 (C-1), 75.7 (C-4), 72.6 (C-2), 71.2 (C-10), 68.2 (C-7), 47.4 (C-3), 43.0 (C-14), 42.5 (C-15), 39.4 (C-8), 34.2 (C-6), 33.4 (C-16), 31.2 (C-methyl of acetonide), 24.9 (C-methyl of acetonide), 20.8 (OAc), 19.5 (C-17), 14.0 (C-19), 13.4 (C-18).

¶ Taxane **7** : HRFABMS *m/z* 421.1838 ($M+Na^+$), calculated for $C_{20}H_{30}O_8Na$, 421.1838; ^1H NMR δ (ppm) 4.35 (1H, s, H-2), 4.27 (1H, d, J=11.1 Hz, H-20a), 4.07 (1H, br.dd, J=9.9, 5.9 Hz, H-5), 4.00 (1H, d, J=12.1 Hz, H-20b), 3.61 (1H, dd, J=12.3, 2.0 Hz, H-7), 2.50 (1H, septet, J=7.0, H-15), 2.39 (1H, s, H-3), 2.34 (1H, o.ddd, J=12, 6.2, 3.0 Hz, H-6a), 2.32 (3H, s, H-14), 2.15 (1H, d, J=13.5 Hz, H-9a), 2.08 (1H, d, J=13.5 Hz, H-9b), 1.93 (3H, s, H-18), 1.84 (1H, q, J=12.3 Hz, H-6b), 1.29 (3H, o.d, J=7.5 Hz, H-17), 1.27 (3H, o.d, J=7.6 Hz, H-16), 1.26 (3H, o.s, H-19); ^{13}C NMR δ (ppm) 212.7 (C-1), 164.0 (C-11), 124.2 (C-12), 113.4 (C-10), 86.2 (C-2), 85.1 (C-4), 84.7 (C-7), 76.8 (C-20), 76.2 (C-5), 57.8 (C-3), 47.8 (C-9), 30.3 (C-6), 26.3 (C-15), 26.0 (C-14), 20.7 (C-16), 20.2 (C-17), 14.8 (C-19), 9.1 (C-18).

rearrangement **6** to **7** is shown in Scheme 1 with the putative intermediates in brackets. The sequence of the reactions could be altered. It involves: (i) an oxidation–reduction of C-10 and C-9 positions giving rise to elimination of acetone; (ii) a retro-cyclization of the C-1 hydroxyl group to form the ring opened ketone; (iii) methoxide induced retro-Claisen at C-13 and isomerization of the double bond C-11/C-15 to C-11/C-12.



Scheme 1. (a) Acetone, DMP, CSA, rt, 1 h; (b) 3×5 equivs. $NaBH_4$, THF/phosphate buffer, pH 7.0, 2/1, 7 h for **3**, 15 equivs. $NaBH_4$, rt, 24 h for both **3** and **4**; (c) Jones' reagent 100 µl, 1 h, 0°C; (d) 6 equivs. NaOMe/MeOH, overnight, 4°C

The new skeleton **7** would enable the investigation of the role of cycles A and B in tubulin binding. In addition, it could be used as a backbone to couple inhibitors of specific cellular targets known to confer resistance to chemotherapeutic agents including taxanes.

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References

1. McGuire, W. P.; Ozols, R. F. In *Seminars in Oncology: Chemotherapy of Advanced Ovarian Cancer*; Grune and Stratton: New York, 1998; Vol. 25, pp. 340–348.

2. Schiff, P. B.; Fant, J.; Horwitz, S. B. *Nature (London)* **1979**, *277*, 665–667.
3. Kingston, D. G. I. In *ACS Symposium Series: Recent Advances in the Chemistry and Structure-Activity Relationships of Paclitaxel (Taxol)* **1995**, *583*, 203–216.
4. Ter Haar, E. *Exp. Opin. Ther. Patents* **1998**, *8 (5)*, 571–586.
5. Zamir, L. O.; Nedea, M. E.; Bélair, S.; Sauriol, F.; Mamer, O.; Jacqmain, E.; Jean, F. I.; Garneau, F. X. *Tetrahedron Lett.* **1992**, *33*, 5173–5176.
6. Gunawardana, G. P.; Premachandran, U.; Burres, N. S.; Whittern, D. N.; Henry, R.; Spanton, S.; McAlpine, J. B. *J. Nat. Prod.* **1992**, *55*, 1686–1689.
7. Zamir, L. O.; Nedea, M. E.; Zhou, Z. H.; Bélair, S.; Caron, G.; Sauriol, F.; Jacqmain, E.; Jean, F. I.; Garneau, F. X.; Mamer, O. *Can. J. Chem.* **1995**, *73*, 655–665.
8. Zamir, L. O.; Zheng, Y. F.; Caron, G.; Sauriol, F.; Mamer, O. *Tetrahedron Lett.* **1996**, *37*, 6435–6438.
9. Zamir, L. O.; Balachandran, S.; Zheng, Y. F.; Nedea, M. E; Caron, G.; Nikolakakis, A.; Vishwakarma, R. A.; Sauriol, F.; Mamer, O. *Tetrahedron* **1997**, *53*, 15991–16008.
10. Py, S.; Khuong-Huu, F. *Bull. Soc. Chim. Fr.* **1993**, *130*, 189–191.
11. Appendino, G.; Jakupovic, J.; Varese, M.; Bombardelli, E. *Tetrahedron Lett.* **1996**, *37*, 727–730.
12. Appendino, G.; Fenoglio, I.; Vander Velde, D. G. *J. Nat. Prod.* **1997**, *60*, 464–466.
13. Klein, L. L. *Tetrahedron Lett.* **1993**, *34*, 2047–2050; Klein, L. L.; Li, L.; Maring, C. J.; Yeung, C. M.; Thomas, S. A.; Grampovnik, D. J.; Plattner, J. J. *J. Med. Chem.* **1995**, *38*, 1482–1492.
14. Walker, D. G.; Standridge, R. T.; Swigor, J. E. *J. Labelled Compd. Radiopharm.* **1995**, *36*, 479–492.