Pergamon

Tetrahedron, Vol. 53, No. 47, pp. 15991-16008, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)10069-2

Acid Catalyzed Rearrangement and Acyl Migration Studies on 9-Dihydro-13-acetylbaccatin-III, A Major Taxane from *Taxus canadensis*

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Abstract: A detailed investigation of the rearrangement of the major taxane from *Taxus canadensis* enables to suggest the sequence of the reactions involved: 9-dihydro-13-acetylbaccatin III → *abeo*-taxanes with intact oxetane and acyl migration → *abeo*-taxanes with intact oxetane and deacylation → *abeo*-taxanes with opening of the oxetane and various acyl migrations including two unusual benzoyl shifts.

Taxus canadensis[1-6] differs from other yews by its appearance (small ramping shrub) and particularly by the content of its taxanes. It does produce paclitaxel (**1**) in the same amounts as other yews. Two taxanes specific to the Canadian yew are: an interesting partly cyclized minor metabolite, canadensene[7,8] and a major compound, 9-dihydro-13-acetylbaccatin-III[5,6](**2**) which can be isolated from the needles. These compounds have only been detected as minor metabolites from only one other yew species : *Taxus chinensis.*[13] 9-Dihydro-13-acetylbaccatin-III is only abundant in *Taxus canadensis*, the Canadian yew growing ubiquitously in Quebec. Regardless of the collection site, its content is five to seven times the amount of paclitaxel and other related taxanes. It is therefore a potential source for semi-synthesis of paclitaxel and related anticancer drugs. Additionally the 9-dihydro-baccatin system has advantages including greater stability due to resistance towards base catalyzed C_7-OH epimerisation and subsequent degradation, and greater water solubility due to an additional hydroxyl group enabling derivatisations. Keeping in view of the relatively higher abundance of compound **2** in *Taxus canadensis* needles and its utility towards synthesis of anti-cancer taxoids, we have undertaken chemical transformation studies on **2** to understand its chemistry and structure activity relationship in order to exploit it for the synthesis of paclitaxel analogues. The chemistry of this compound and in particular rearrangement reactions, were therefore investigated. Taxanes with ring A contracted to a five membered ring or 11(15→1)-*abeo*-taxanes have been found in a few yew species.[9a,b] In fact, the revised structure of brevifoliol[9c] demonstrates that it is perhaps the first *abeo*-

taxane isolated. In addition, the chemical conversion of paclitaxel and 10-deacetylbaccatin-III into *abeo*-taxanes has been successfully achieved[9a,10] and related studies have been reported. [9d-f] Rearranged paclitaxel seems to retain biological activity according to the microtubule assay.[10]

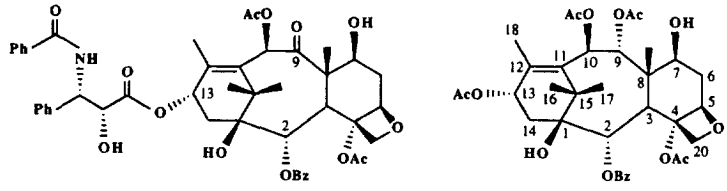


Fig. 1. Paclitaxel and *Taxus canadensis* abundant taxane: 9-dihydro-13-acetylbaccatin III

In this publication we have confirmed the preliminary evidence[11] that the rearrangement of 9-dihydro-13-acetylbaccatin III precedes the oxetane opening. The new 11(15→1)-*abeo*-taxanes which were characterized suggested plausible sequences of the events involved. In addition, two very unusual benzoyl shifts are reported *when the oxetane ring is opened.* We are also reporting the first isolation from the needles of *Taxus canadensis* of an *abeo*-taxane: wallifoliol, which was detected previously in *Taxus wallichiana.*[12] This natural product not only has ring A but also ring B contracted.

EXPERIMENTAL

Isolation and purification of 9-dihydro-13-acetylbaccatin III (2)

9-Dihydro-13-acetylbaccatin III (**2**) was isolated and purified according to reported procedures.[2,4]

NMR and Mass Spectrometry Measurements

^{1}H, ^{13}C, HMQC, HMBC and NOESY NMR spectral data were obtained on a Varian UNITY 500 spectrometer operating at 499.84 MHz for proton and 125.69 MHz for carbon-13. The spectra were obtained on 1-2 mg samples dissolved in $CDCl_3$ which was used as the internal reference. In the proton NMR spectra, the multiplicity shown in the tables is the apparent one. The low resolution xenon fast atom bombardment (FAB) mass spectra were obtained in glycerol, with a VG ZAB-MS instrument. Samples were dissolved in 0.2 µl DMSO before addition of 0.5 µl of glycerol. The high resolution FAB mass spectra were obtained similarly in glycerol-DMSO, at a resolving power of 12000. The electrospray mass spectra were obtained in negative mode by dissolving the sample in 20 mM triethylamine- isopropanol, using isopropanol as the mobile phase at a flow rate of 10 µl/min.

High Performance Liquid Chromatography Conditions

Preparative and semi-preparative HPLC was performed on a Waters Delta Prep 3000 instrument coupled with a Model 481 variable wavelength detector set at 227nm (Waters) and a Perkin-Elmer 024 plotter. Preparative HPLC was performed with one partisil 10 ODS-2 MAG 20 reversed phase column (22 x 500 mm, Whatman) at a flow rate of 18 ml/min. Semi-preparative HPLC was performed with two partisil 10 ODS-2 MAG 9 reversed phase columns connected in series (9.4 x 250 mm, Whatman). For all the preparative HPLC, a gradient of acetonitrile (25-100 %) in water over 100 min or 120 min was used. The analytical HPLC system used was the Waters 600E multi solvent delivery system coupled to a Waters 996 photo diode array detector set at 227 nm, using two partisil ODS-2 columns (4.6 x 250 mm) connected in series. The data was processed with the Millenium 2010 software. A gradient of acetonitrile (25-100 %) in water over 50 min, at a flow rate of 1 ml/min was used.

9-Dihydro-13-acetyl-7,9-isopropylidene-baccatin-III (3)

To a solution of compound **2** (118 mg, 0.187 mmol) in acetone (70 ml) was added dimethoxypropane (3 ml, 24.4 mmol) and *para*-toluene sulfonic acid monohydrate (*p*-TSA·H_2O) (88 mg, 0.462 mmol). The mixture was stirred at room temperature for 1 hr (TLC monitoring showed only one product), water (10 ml) was added and the mixture was extracted with diethyl ether (3 x 40 ml). The organic phase was washed with 10 % $NaHCO_3$ (10 ml), saturated NaCl (10 ml), dried over anhydrous Na_2SO_4 and the solvent was removed. The flash column chromatography using hexane-ethyl acetate (1:1) gave compound **3** (113 mg, 90 %). The homogeneity of **3** was confirmed by analytical HPLC (R_t = 41.27 min). The NMR data were in complete agreement with the literature.[14]

Preparation of compounds 4, 5 and 6

A mixture of compound **2** (28 mg, 0.044 mmol), 2,2-dimethoxypropane (0.70 ml, 5.7 mmol) and *p*-TSA·H_2O (25 mg, 0.13 mmol) in acetone (25 ml) was stirred at room temperature for 72 hrs, water (5 ml) was added and the mixture was extracted with diethyl ether (3 x 30 ml). The combined organic phase was washed with saturated $NaHCO_3$ (15 ml), brine (15 ml), dried over Na_2SO_4 and concentrated to give a residue which was purified by silica gel flash column chromatography using hexane-ethyl acetate (7:3) to give a mixture (TLC R_f = 0.72) containing compounds **4**, **5** and **6** (total 27 mg, 83 %). The analytical HPLC (RP-18 column, 25-100 % CH_3CN in H_2O gradient over 50 min) of this mixture showed three peaks (R_t = 44.3 min. for **4**, overlapping peaks at R_t = 46.0 min. for **5** and **6**). The preparative HPLC separated compound **4** (18 mg, 23 % overall yield). The mixture of compound **5** and **6** was purified by flash column chromatography using CH_2Cl_2-ethyl acetate (4:1) to give pure **5** (7 mg, 21 %) and 6 (4 mg, 13 %).

2α-Benzoyl-4α,10β,13α-triacetoxy-15-hydroxy-20,5β-7β,9α-diisopropylidene-11(12)-ene-11(15->1)-abeo-taxane (4)

FAB-MS: M^+Na: 751.33056; $C_{39}H_{52}O_{13}Na$ requires 751.33056; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.0 Hz, 2H, *ortho* of Ph), 7.51 (t, *J* = 7.3 Hz, 1H, *para* of Ph), 7.40 (t, *J* = 7.3 Hz, 2H, *meta* of Ph), 6.58 (d, *J* = 10.0 Hz, 1H, H-10), 5.92 (d, *J* = 6.6 Hz, 1H, H-2), 5.59 (brt, *J* = 7.3 Hz, 1H, H-13), 5.21 (brt, *J*= 2.6 Hz, 1H,

H-5), 4.43 (d, J = 10.0 Hz, 1H, H-9), 4.24 (d, J = 9.3 Hz, 1H, H-20a), 4.01 (dd, J = 11.5, 4.4 Hz, 1H, H-7), 3.61 (d, J = 9.2 Hz, 1H, H-20b), 3.08 (d, J = 6.8 Hz, 1H, H-3), 2.93 (s, 1H, OH-15), 2.59 (dd, J = 14.7, 7.3 Hz, 1H, H-14a), 2.55 (dd, J = 14.9, 7.3 Hz, 1H, H-14b), 2.14 (s, 3H, OAc), 2.11 (s, 3H, OAc), 2.09 (s, 3H, OAc), 2.03 (d, J = 1.0 Hz, 3H, Me-18), 1.88 (m, 1H, H-6a), 1.77 (ddd, J = 14.2, 11.5, 2.2 Hz, 1H, H-6b), 1.57 (s, 3H, Me), 1.55 (s, 3H, Me-19), 1.42 (s, 3H), 1.12 (s, 3H), 0.85 (s, 3H). ^{13}C-NMR ($CDCl_3$, HMQC data) 68.6 (C-1), 71.6 (C-2), 42.3 (C-3), 82.7 (C-4), 74.3 (C-5), 29.9 (C-6), 64.9 (C-7), 39.6 (C-8), 79.6 (C-9), 70.2 (C-10), 137.9 (C-11), 145.2 (C-12), 80.4 (C-13), 36.4 (C-14), 74.8 (C-15), 27.9 (C-16 or C-17), 26.7 (C-17 or C-16), 11.7 (C-18), 14.1 (C-19), 67.8 (C-20), 24.7, 30.8, 99.4 (9-O-C(Me_2)-O-7), 26.7, 26.4, 107.7 (20-O-C(Me)-O-5), 20.8/169.3 (Ac), 20.8/168.4 (Ac), 20.8/170.7 (Ac), 168.4 (benzoyl carbonyl), 130.0 (C2,6 of benzoyl ring), 127.9 (C3,5 of benzoyl ring), 132.8 (C4 of benzoyl ring).

2α-Benzoyl-4α,7β,13α-triacetoxy-15-hydroxy-20,5β-9α,10β-diisopropylidene-11(12)-ene-11(15->1)-abeo-taxane **(5)**

FAB-MS: M$^+$Na: 751.33056; $C_{39}H_{52}O_{13}Na$ requires 751.33056; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 8.5 Hz, 2H, *ortho* of Ph), 7.52 (t, J = 7.6 Hz, 1H, *para* of Ph), 7.41 (t, J = 7.6 Hz, 2H, *meta* of Ph), 5.89 (d, J = 6.1 Hz, 1H, H-2), 5.69 (t, J = 7.3 Hz, 1H, H-13), 5.38 (dd, J = 11.7, 5.1 Hz, 1H, H-7), 5.19 (dd, J = 3.7, 2.2 Hz, 1H, H-5), 4.61 (d, J = 9.8 Hz, 1H, H-9), 4.59 (d, J = 9.9 Hz, 1H, H-10), 4.31 (d, J = 9.2 Hz, 1H, H-20a), 3.58 (d, J = 9.0 Hz, 1H, H-20b), 2.95 (d, J = 6.3 Hz, 1H, H-3), 2.56 (dd, J = 14.4, 7.1 Hz, 1H, H-14a), 2.53 (s, 1H, OH-15), 2.49 (dd, J = 14.4, 7.1 Hz, 1H, H-14b), 2.13 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.00 (s, 3H, OAc), 1.93 (s , 3H, Me-18), 1.88 (dt, J = 14.4, 4.6, 4.6 Hz, 1H, H-6a), 1.81 (ddd, J = 14.9, 11.7, 2.4 Hz, 1H, H-6b), 1.60 (s, 3H, Me-19), 1.37 (s, 3H), 1.36 (s, 3H), 1.17 (s, 3H, Me-16/17), 1.13 (s, 3H, Me-17/16), 1.12 (s, 3H), 0.87 (s, 3H). ^{13}C-NMR ($CDCl_3$, HMQC data) 76.2 (C-1), 72.6 (C-2), 44.7 (C-3), 81.5 (C-4), 74.3 (C-5), 30.1 (C-6), 66.7 (C-7), 42.4 (C-8), 82.4 (C-9), 71.7 (C-10), 136.7 (C-11), 146.7 (C-12), 80.4 (C-13), 37.7 (C-14), 70.0 (C-15), 28.2 (C-16 or C-17), 24.9 (C-17 or C-16), 11.6 (C-18), 13.5 (C-19), 67.5 (C-20), 26.5, 26.3, 108.4 (9-O-C(Me_2)-O-10), 26.3, 25.9, 108.4 (20-O-C(Me_2)-O-5), 20.7/169.3 (Ac), 21.4/170.3 (Ac), 20.8/170.9 (Ac), 168.7 (benzoyl carbonyl), 130.2 (C2,6 of benzoyl ring), 128.2 (C3,5 of benzoyl ring), 132.7 (C4 of benzoyl ring).

2α-Benzoyl-7β,13α,20-triacetoxy-15-hydroxy-4α,5β-9α,10β-diisopropylidene-11(12)-ene-11(15->1)-abeo-taxane **(6)** (Scheme 1, Table 1, Fig. 2)

FAB-MS: M$^+$Na: 751.33056; $C_{39}H_{52}O_{13}Na$ requires 751.33056; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.05 (d, J = 8.5 Hz, 2H, *ortho* of Ph), 7.56 (t, J = 7.6 Hz, 1H, *para* of Ph), 7.45 (t, J = 7.6 Hz, 2H, *meta* of Ph), 6.10 (d, J = 7.8 Hz, 1H, H-2), 5.68 (t, J = 7.1 Hz, 1H, H-13), 5.41 (dd, J = 11.5, 5.6 Hz, 1H, H-7), 4.64 (d, J = 10.0 Hz, 1H, H-10), 4.48 (d, J = 10.0 Hz, 1H, H-9), 4.27 (d, J = 12.5 Hz, 1H, H-20a), 4.27 (dd, J = 4.6, 2.0 Hz, 1H, H-5), 4.09 (d, J = 12.4 Hz, 1H, H-20b), 2.54 (dd, J = 14.1, 7.8 Hz, 1H, H-14a), 2.49 (dd, J = 14.0, 6.8 Hz, 1H, H-14b), 2.34 (d, J = 7.8 Hz, 1H, H-3), 2.15 (o. m, 1H, H-6a), 2.08 (s, 3H, OAc), 2.02 (s, 3H, OAc), 1.98 (om, 1H, H-6b), 1.90 (d, J = 0.7 Hz, 3H, Me-18), 1.69 (s, 3H, OAc), 1.55 (s, 3H), 1.42 (s, 3H, Me-19), 1.37 (s, 3H), 1.35 (s, 3H), 1.24

(s, 3H), 1.12 (s, 3H, Me-17/16), 1.10 (s, 3H, Me-16/17). ^{13}C-NMR ($CDCl_3$, HMQC data) 76.5 (C-1), 69.6 (C-2), 167.2 (C-2, C=O), 50.8 (C-3), 80.2 (C-4), 75.7 (C-5), 28.2 (C-6), 67.5 (C-7), 41.0 (C-8), 81.9 (C-9),71.0 (C-10), 135.1 (C-11), 147.8 (C-12), 79.3 (C-13), 170.7 (C-13, C=O), 37.3 (C-14), 69.5 (C-15), 24.1 (C-16 or C-17), 28.5 (C-17 or C-16), 11.5 (C-18), 13.5 (C-19), 64.3 (C-20), 20.8/170.7 (Ac), 21.4/170.3 (Ac), 19.9/167.9 (Ac), 108.04, 29.4, 29.4 (O=C(Me_2)-O), 107.7, 26.4, 26.4 (O=C(Me_2)-O), 167.2 (benzoyl carbonyl), 130.0 (C2,6 of benzoyl ring), 128.3 (C3,5 of benzoyl ring), 132.9 (C4 of benzoyl ring). All compounds (**4-6**) were completely analyzed by COSY, NOESY, HMQC and HMBC experiments.

Preparation of compounds (7), (8) and (9)

The reaction mixture of compound **2** (20 mg, 0.031 mmole) and *p*-TSA.H_2O (18 mg, 0.095 mmol, 3 equiv) in MeOH (5 ml) was stirred at room temperature for 24 hrs. Compound **2** was initially insoluble but the reaction mixture became homogeneous after a few hours. After 24 hrs ethyl acetate (20 ml) and water (20 ml) were added, the phases separated and the aqueous phase was further extracted with ethyl acetate (2 x 20 ml). The combined organic phase was dried (Mg SO_4) and concentrated under reduced pressure to give a mixture of three major compounds (41 mg, overall 82 % yield) which were purified by preparative reversed phase HPLC (25-100 % CH_3CN in H_2O, 120 min gradient) to provide compound **7** (9 mg, 18 % yield, R_t = 45.5 min.), **8** (14 mg, 28 % yield, R_t = 36.5 min.), **9** (14 mg, 28 % yield, R_t = 25.5 min.). The compounds **7**, **8** and **9** were fully characterized by NMR and MS data.

2α-Benzoyl-4α,7β,13α-triacetoxy-9α,10β,15-trihydroxy-11(12)-ene-20,5-epoxy-11(15->1)-abeo-taxane (**7**)

FAB-MS: $(M+H)^+$: 631.27567; $C_{33}H_{43}O_{12}$ requires 631.27545; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.3 Hz, 2H, *ortho* of Ph), 7.60 (t, *J* = 7.3 Hz, 1H, *para* of Ph), 7.47 (t, *J* = 7.8 Hz, 2H, *meta* of Ph), 6.03 (d, *J* = 7.3 Hz, 1H, H-2), 4.61 (br d, *J* = 9.3 Hz, 1H, H-10), 5.72 (br t, *J* = 7.1 Hz, 1H, H-13), 4.34 (br d, *J* = 9.0 Hz, 1H, H-9), 5.35 (t, *J* = 8.2 Hz, 1H, H-7), 4.93 (d, J = 8.0 Hz, 1H, H-5), 4.46 (d, J = 7.8 Hz, 1H, H-20a), 4.11 (br d, J = 7.5 Hz, 1H, H-20b), 2.95 (br d, *J* = 7.1 Hz, 1H, H-3), 2.29 (dd, *J* = 7.1, 14.1 Hz, 1H, H-14a), 1.85 (o.m, 1H, H-14b), 2.60 (dt, J = 16.6, 7.6, 7.6 Hz, 1H, H-6a), 1.85 (o.m, 1H, H-6b), 1.88 (s, 3H, Me-19 or 18), 1.93 (s, 3H, Me-18 or 19), 1.12 (s, 3H, Me-17 or 16), 1.09 (s, 3H, Me-16 or 17). 2.95 (o br s, OH-9), 2.15 (s, 6H, 2 x CO*Me*), 2.06 (s, 3H, CO*Me*).The assignments for compound (**7**) were confirmed by COSY, HMQC and HMBC experiments.

2α-Benzoyl-4α,13α-diacetoxy-7β,9α,10β,15-tetrahydroxy-11(12)-ene-20,5-epoxy-11(15->1)-abeo-taxane (**8**)

ESMS (negative ion) : M^+: 588.3; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.1 Hz, 2H, *ortho* of Ph), 7.60 (t, *J* = 7.6 Hz, 1H, *para* of Ph), 7.47 (t, *J* = 7.6 Hz, 2H, *meta* of Ph), 6.10 (d, *J* = 7.6 Hz, 1H, H-2), 5.73 (br t, *J* = 7.1 Hz, 1H, H-13), 4.52 (br dd, *J* = 9.0, 6.1 Hz, 1H, H-10), 3.78 (br d, J = 5.6 Hz, OH-10), 4.37 (br dd, *J* = 10.0, 3.2 Hz, 1H, H-9), 4.24 (o, 1H, OH-9), 4.24 (t, *J* = 8.5 Hz, 1H, H-7), 4.93 (d, J = 8.3 Hz, 1H, H-5), 4.43 (d, J = 7.8 Hz, 1H, H-20a), 4.09 (d, J = 7.6 Hz, 1H, H-20b), 4.24 (br, OH-9), 3.61 (br d, J = 5.6 Hz, OH-10), 2.85 (d, *J* = 7.3 Hz, 1H, H-3), 2.27 (dd, *J* = 7.3, 14.2 Hz, 1H, H-14a), 1.90 (o.m, 1H, H-14b), 2.59 (dt, J = 15.4, 8.0, 8.0

Hz, 1H, H-6a), 1.86 (o.m, 1H, H-6b), 1.87 (s, 3H, Me-18), 1.88 (s, 3H, Me-19), 1.23 (o s, Me-17), 1.14 (s, Me-16), 2.15 (s, 3H, CO*Me*), 2.16 (s, 3H, CO*Me*); ^{13}C-NMR ($CDCl_3$, HMQC and HMBC data) 76.5 (C-1), 68.4 (C-2), 79.7 (C-4), 84.5 (C-5), 44.6 (C-3), 72.5 (C-7), 37.6 (C-6), 42.2 (C-8), 80.4 (C-9), 68.4 (C-10), 143.9 (C-11 or 12), 138.8 (C-12 or 11), 79.0 (C-13), 36.4 (C-14), 67.6 (C-15), 27.9 (C-16), 24.9 (C-17), 11.7 (C-19), 11.4 (C-18), 74.3 (C-20), 20.8/170.9 (Ac), 21.7/168.9 (Ac). The assignments for compound (**8**) were confirmed by COSY, HMQC and HMBC experiments.

20-Benzoyl-5α,13α-diacetoxy-2α,4α,7β,9α,10β,15-hexahydroxy-11(12)-ene-11(15->1)-abeo-taxane (**9**):

Compound **9** was fully characterized as *20-benzoyl-5α,13α-diacetoxy-2α,4α,7β,9α,10β,15-hexahydroxy-11(12)-ene-11(15->1)-abeo-taxane* by NMR (Table 3). The high resolution mass spectra (electrospray mass spectra negative mode) are in agreement with this structure ES-MS (negative ion) : M^+: 606.3. The assignments for compound (**9**) were confirmed by COSY, NOESY HMQC and HMBC experiments.

Preparation of compound (10)

Compound**2** (20 mg, 0.031 mmole) was mixed with *p*-TSA H_2O (18 mg, 0.095 mmol, 3 equiv) in MeOH (5 ml) and stirred at room temperature for 72 hrs. The reaction mixture gives a clear solution within a few hours. After 72 hrs, ethyl acetate (20 ml) and water (20 ml) were added and the phases separated. The aqueous phase was further extracted with ethyl acetate (2 x 20 ml). The combined organic phase was dried (Mg SO_4 anhydrous) and evaporated. The resulting solid showed one major spot on silica TLC plates (R_f = 0.11 in 10 % MeOH in CH_2Cl_2). The silica gel flash column (10 % MeOH in CH_2Cl_2) provided a pure compound, 2α-benzoyl-13β-methoxy-4α,5α,7β,9α,10β,15,20-heptahydroxy-11(12)-ene-11(15->1)-*abeo*-taxane (**10**) in 40 % yield . The structure was fully characterized by NMR (Table 2). The high resolution mass spectral data confirmed it. FAB-MS: M^+Na: 559.25195; $C_{28}H_{40}O_{10}Na$ requires 559.25192;

20-Benzoyl-13β-methoxy-2α,4α,5α,7β,9α,10β,15-heptahydroxy-11(12)-ene-11(15->1)-abeo-taxane (11)

Compound **8** (3.6 mg, 0.006 mmole) was dissolved in MeOH (1.0 ml) and *para*- toluene sulfonic acid monohydrate (*p*-TSA.H_2O, 3.4 mg, 0.018 mmole, 3 equiv) was added and the mixture was stirred at room temperature. After 48 hrs, water (10 ml) was added and extracted with ethyl acetate (3 x 15 ml). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a solid product. This was subjected to HPLC and mainly one compound (**11**, 1.4 mg) was obtained in 44 % yield. Compound **11** was fully characterized as 20-benzoyl-13β-methoxy-2α,4α,5α,7β,9α,10β,15-heptahydroxy-11(12)-ene-11(15->1)-*abeo*-taxane by NMR (Table 4). The low resolution and high resolution mass spectroscopy data are in agreement with this structure: FAB-MS: $(M+Na)^+$: 559.25195; $C_{28}H_{40}O_{10}Na$ requires 559.25192;

Isolation and purification of T. canadensis wallifoliol (12 , Fig.3)

Fresh needles of *T. canadensis* (240 g) were extracted with a mixture of methanol:dichloromethane (1:1, 1.8 L). The extraction was carried out at room temperature for 18 hrs with constant agitation. The extract was

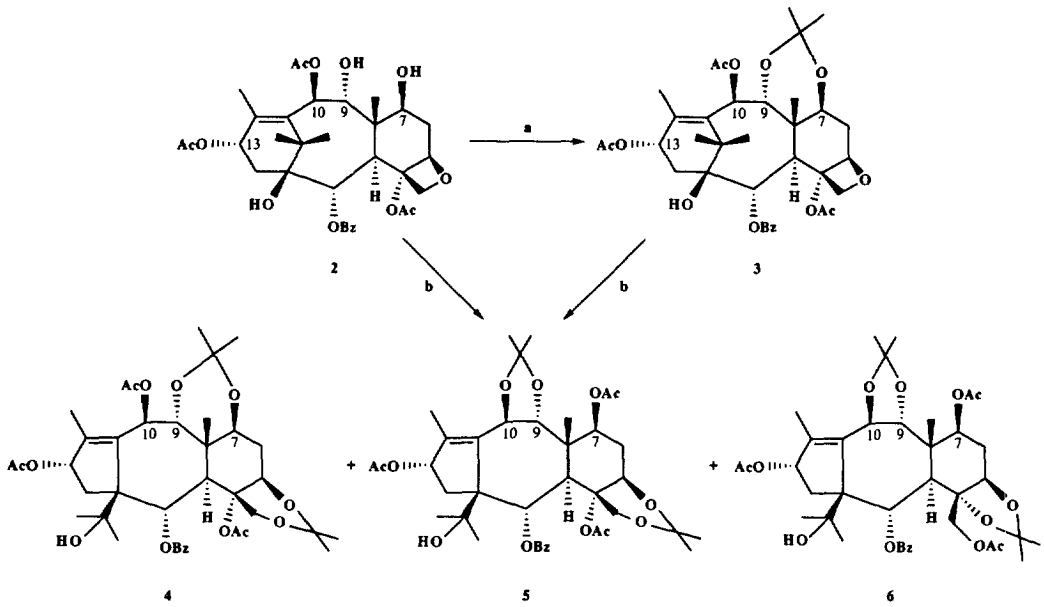
then filtered and evaporated to obtain a solid mass of which 18.0 g were made into a slurry using celite (80 g). Column chromatography was carried out over silica gel (150 g). Initially, the column was eluted with 2.0 L dichloromethane: ethyl acetate (85:15) and fractions 1-24 were collected. The column was further eluted with 2.8 L of hexane:acetone (65:35) and fractions 25-53 were collected. Fraction 51 which contained mainly 10-deacetylbaccatin III was evaporated and subjected to preparative HPLC using 120 min gradient. 10-Deacetylbaccatin III elutes at R_t 22.5 min. The fraction between R_t 24-27 min. was collected, evaporated and reinjected on the semi-preparative HPLC under isocratic conditions using acetonitrile:water (31:69) at 3 ml/min. The peak at R_t 25.4 min. was collected and evaporated to yield a pure compound . It was fully characterized as wallifoliol[12] (**12**, Fig. 3) by NMR (Table 5). The low resolution and high resolution mass spectroscopy data are in agreement with this structure: FAB-MS: $(M+H)^+$: 543.22324; $C_{29}H_{35}O_{10}$ requires 543.22302.

RESULTS AND DISCUSSION

The accumulation of 9-dihydro-13-acetylbaccatin III (**2**, Fig. 1) is specific to the needles of the Canadian yew. It has only been reported as a minor metabolite in the bark of *Taxus chinensis*.[13] In this publication, we are reporting studies of the mechanisms of the Wagner-Meerwein acid rearrangements of 9-dihydro-13-acetylbaccatin III. Two unusual benzoyl shifts, intramolecular acetyl migration, opening of the oxetane and the characterization of an *abeo*-taxane isolated from the needles of *Taxus canadensis* for the first time, will be discussed.

Acetyl migrations and opening of the oxetane during rearrangements.

In a preliminary publication,[11] we reported that 9-dihydro-13-acetylbaccatin III (**2**, Fig. 1 and Scheme 1) under acidic conditions can lead to a mixture of *abeo*-taxanes where the *oxetane ring* is opened and various acetyl migrations occur. This reaction was discovered during the preparation of the acetonide, 9-dihydro-13-acetyl-7,9-isopropylidene-baccatin III (**3**, Scheme 1), when inadvertently, compound **2** was forgotten at room temperature for 72 hours with DMP and *p*-TSA in acetone, instead of one hour! In 72 hours no traces of the acetonide **3** (which is easily obtained in 90% yield from **2** in an hour under these conditions) could be found. In thin layer chromatography what appeared to be one compound was observed. However ^{1}H-NMR analysis revealed that it consisted mainly of three *abeo*-taxanes. Separation on preparative HPLC and flash chromatography (silica gel) yielded *abeo*-taxanes (**4**) (23%), (**5**) (20%) and (**6**) (12%) (Scheme 1). The low resolution FAB-MS of **4**, **5** and **6** showed identical fragmentations : 729 (MH^+), 711(MH^+-H_2O) and 669 (MH^+-AcOH). In addition, the high resolution mass spectra of the three compounds were also the same: M^+Na, 751.33056, $C_{39}H_{52}O_{13}Na$, requires 751.33056, confirming that they were regioisomers. Extensive NMR studies on **4**, **5** and **6** clearly established their structures as shown in Scheme 1.



Scheme 1. Chemical structures of the acid rearrangements of 9-dihydro-13-acetylbaccatin III (**2**) and its acetonide (**3**) involving acetyl migrations and opening of the oxetane. The reaction conditions are the following: a) *p*-TSA.H_2O (3 eq.), DMP (130 eq.), Acetone,R.T., 1 hr.; (b) *p*-TSA.H_2O (3 eq.), DMP (130 eq.), Acetone,R.T., 72 hrs.

In the structure analysis of **4**, the placement of two isopropylidene groups (7β, 9α and 20, 5β) were assigned by HMBC data which showed correlations between one isopropyl C-2 carbon (99.4) with H-7 (4.00) and H-9 (4.43), the second isopropyl C-2 carbon (107.7) with H-20a (4.24), H-20b (3.61) and H-5 (5.21) respectively. The 10-β OAc was assigned by HMBC correlation between acetyl carbonyl (168.4) with H-10 (6.58). Similarily the structure of compound **5** was determined and placement of one isopropylidene at 9α and 10β position was ascertained by the observation of a strong NOE between H-10 (4.59) and isopropyl-methyl groups (1.33). The 7β-OAc was assigned by HMBC correlation between acetyl carbonyl (170.3) and H-7 (5.38). Stereochemical details were determined by detailed NOESY data analysis (Table 1). The important and distinct feature of the structure of compound **6** was the presence of 4α, 5β-isopropylidene group which was confirmed by HMBC (Fig. 2).

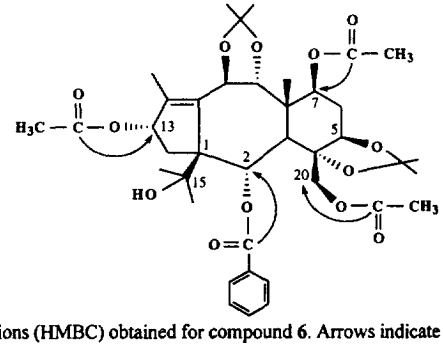


Fig. 2. Two-dimensional ^1H-^{13}C correlations (HMBC) obtained for compound **6**. Arrows indicate carbon-hydrogen connectivities. Arrow head indicates location of proton.

Table 1. NOESY observed on compound **6** (NOE positive cross peaks)

Proton	NOE observed: s (strong), m (medium), w (weak)
H-2	**H-9 (s), Me-19 (s), Me-17 (s), H-20a/H-5 (w)**
H-3	**H-7 (s), H-14a (s), H10 (w)**
H-5/H-20a	**H-20b (s), H-6b (s), Me 19 (s), Me 1.23 (from blocking group 1) (s)**
H-6a	**H-7 (m), H-6b (s)**
H-7	**H-10 (s), H-6b (s), H-3 (s)**
H-10	**H-7 (s), H-3 (m), Me-18 (s), Me 1.35 (from blocking group 2) (s)**
H-13	**Me-16 (s), H-14a (m), H-14b (w), Me-18 (w)**
H-14a	**H-14b (s), H-13 (m)**
H-14b	**H-14a (s), Me-16 (m), H-13 (m)**
Me 16	**H-13 (m)**
Me 17	**H-14b (s), H-2 (s)**
Me-18	**H-10 (s), H-13 (w)**
Me-19	**H-2 (s), H-20a/H-5 (s), H-9 (s), H-6b (s), H-20b (w)**
H-20b	**H-20a (s), Me 1.23 (from blocking group 1) (s) H-2 (w), H-19 (w)**
Me_2C-O,O	
1.55ppm(1)	**Me 1.23(from blocking group 1) (s) H-3 (w), H-6b(w)**
1.23ppm(1)	**H-20a/H-5 (s), Me 1.55(from blocking group 1) (s), H-20b (w)**
Me_2C-O,O	
1.37 ppm (2)	**H-9 (s)**
1.35 ppm (2)	

In order to determine if the acetonide (**3**) was a reaction intermediate, it was subjected to the same acidic conditions for 72 hours. As expected it gave the same mixture of *abeo*-taxanes (**4**), (**5**) and (**6**) in the same ratio (Scheme 1). Only two of the rearranged products (**5** and **6**) were obtained when the acid catalyst (*p*-TSA) was used in acetone without DMP. This result suggests that the formation of the acetonide follows the acetyl migration from C-10 to C-9 to C-7 when acetone *only* was used. However, when the more reactive DMP was used, compound (**4**) was observed implying that acetonide formation at C-7, C-9 is faster than acetyl migration. Taxanes (**5**) and (**6**) were probably derived from (**4**) by intramolecular migration of one acetyl group from C-10 to C-7 (to form **5**) and of two acetyl groups from C-10 to C-7 and C-4 to C-20 (to form **6**).[6,10,15,16]

Acid rearrangement versus opening of the oxetane

Preliminary work[11] showed that reaction of 9-dihydro-13-acetylbaccatin III (**2**) in acidic conditions (*p*-TSA in methanol, 72 hrs) led to the *abeo*-taxane **10** (Scheme 2) in which the oxetane has been opened. In addition, deacetylations have occurred at positions C-4, C-10 and the C-13 position was found to be β-methoxylated. In addition, we had indication that if the reaction is stopped after 24 hours non characterized *abeo*-taxanes were obtained with *intact* oxetane rings, but differing in the positions of the acetates. These data suggested that the rearrangement of taxane **2** to *abeo*-taxanes precedes the opening of the oxetane ring. This is in agreement with

the reported conversion of 10-deacetylbaccatin III and paclitaxel into *abeo*-taxanes.[6,7a] This is particularly important, because one can therefore preserve the oxetane which is essential for biological activity while modifying other parts of the molecule.

It was therefore important to study in detail the structure of the rearrangement products of 9-dihydro-13-acetylbaccatin III (**2**) and try to understand the steps involved. The product from the reaction of 9-dihydro-13-acetylbaccatin-III (**2**) with p-TSA·H_2O in MeOH for 72 hrs was rigorously characterized as 2α-benzoyl-13β-methoxy-4α,5α,7β,9α,10β,15,20-heptahydroxy-11(12)-ene-11(15->1)-*abeo*-taxane (compound **10**, Scheme 2) by extensive NMR data (^1H, ^{13}C, HMQC, HMBC and NOESY experiments) and was confirmed by high resolution FABMS.

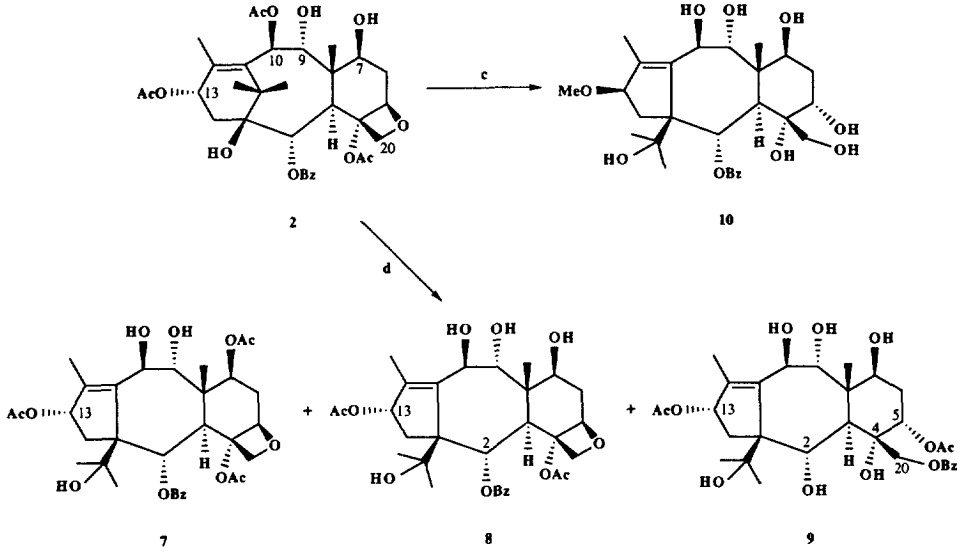
Table 2. Proton and Carbon-13 NMR Data for compound **10**

Position	δ ^1H ppm	M[a]	J (Hz)	δ ^{13}C[b] ppm	Position	δ ^1H ppm	M[a]	J (Hz)	δ ^{13}C[b] ppm
1	--			**76.9**	14a	2.55	dd	14.2;7.3	34.9
2	5.99	d	7.3	70.7	14b	2.12	dd	14.2;7.1	
3	2.93	d	6.8	43.7	15	--			**68.1**
4	--				16/17	1.12	s		25.3
5	3.76	br.s		70.2	17/16	1.08	s		28.2
6a	2.02	br.m		32.9	18	1.92	s		11.5
6b	1.72	br.m			19	1.32	s		13.8
7	4.19	br.d	6.3	68.4	20a/b	3.49	s		62.2
8	--			**42.9**	Bz				
9	4.25	d	10.3	80.7	C2,6	8.03	d	7.3	129.5
10	4.59	br.d	8.3	68.7	C3,5	7.47	t	7.8	128.9
11	--			**138.1**	C4	7,59	t	7.3	133.6
12	--			**145.9**	OMe	3.41	s		55.8
13	4.33	t	6.8	86.3					

[a] M: multiplicity; o:overlap; s:singlet; d: doublet; t:triplet; br.m: broad multiplet
[b] The ^{13}C chemical shifts have been extracted from the HMQC experiment (±0.2 ppm). The numbers in bold character represent quaternary carbons; their shifts have been obtained fromthe HMBC experiment (±0.2ppm)

The NMR data (Table 2) showed the presence of *abeo*-taxane skeleton with four C-methyls (1.08, 1.12, 1.32 and 1.92), a benzoyl group (8.03, 7.59 and 7.47), all three acetyls were found missing in **10**, and one additional methoxyl group (3.41) had appeared. The opening of the oxetane ring was evidenced by the disappearance of the AB quartet typical of two C-20 protons of taxanes. The 11(15->1)-*abeo*-taxane structure was confirmed by the presence of a characteristic and unusually low field signal for C-1 at 76.9 ppm in ^{13}C NMR and also by HMBC correlations of C-1(76.9), C-15 (68.1) and Me-16/17 (28.2/ 25.3) with protons of Me-16/17 (1.12 and 1.08). The placement of -OMe at C-13 position was deduced from HMBC correlation between C-13 (86.3) and methoxyl proton singlet (3.41). The 13-OMe showed very strong NOE with H-20, small NOE with Me-16/17

and weak NOE with Me-19 which supported β-stereochemistry of OMe group. The H-5 showed very strong NOE with H-20 and small NOE with Me-19 confirming 5-αOH, and strong Me-19/ H-2/H-20 NOEs confirmed their β-stereochemistry. The H-2/H-9/Me-19 showed NOEs together confirming 2α-OBz, 9α-OH and 19-βMe assignments. The detailed NOESY and HMBC data analysis unambiguously confirmed the stereochemistry of **10** (as shown in Scheme 2) which indicated that A/B ring rearrangement, complete deacetylation and oxetane ring opening had occurred in 72 hrs. Therefore, in order to elucidate the sequence of these multiple reactions, and to trap intermediate *en route*, the reaction conditions were optimized. It was found that at 24 hrs reaction time, three new major compounds were formed. Purification by preparative HPLC led to three new intermediates **7**, **8** and **9** (Scheme 2).



Scheme 2. Acid rearrangements versus opening of the oxetane: The reaction conditions are the following: c) *p*-TSA.H_2O (3 eq.), MeOH, RT ., 72 hrs reaction and (d) *p*-TSA.H_2O (3 eq.), MeOH, RT, 24 hrs . The 72 hrs reaction leads to formation of an *abeo*-taxane and opening of the oxetane (**10**). The oxetane remains in two of the compounds produced after 24 hrs (d) (**7**, **8**). In **9** an unusual benzoyl shift is added

The NMR and MS data analysis immediately revealed that A/B rearrangement had occurred in all three compounds. The oxetane ring remained intact in **7** and **8**. An intramolecular acetyl migration had occurred in taxane **7** and a deacetylation in **8**. In compound **9**, the oxetane had opened, the acetyl migrated from C-4 to C-5 with epimerisation at C-5. The most surprising feature of compound **9** is a benzoyl group which had shifted from the oxygen at C-2 to the primary alcohol at C-20! The structures of **7**, **8** and **9** were unambiguously assigned by various NMR (^1H, ^{13}C, HMQC, HMBC and NOESY) and MS spectral data analysis. The assignments for **7** and **8** were straightforward as both compounds had undergone the rearrangement to give 11(15->1)-*abeo*-taxane structure and other structural features were preserved, except that in **7** the 10-OAc had migrated to C-7 position (HMBC and NOE data), and in compound **8** this 7-OAc was eventually lost. Intramolecular acetyl migrations for other taxanes have also been reported.[10, 15,16] The structures of **7** and **8** suggested that the following mechanistic

steps : (i) an A/B ring rearrangement (ii) an acyl migration from 10 to 7 position (iii) removal of 7-acetate, preceded the opening of the oxetane ring. It is more difficult to understand the subsequent reactions. A deacetylation at C-4 and methanolysis at C-13 would give compound **10.** In compound **9** two intramolecular acyl transfers have occurred: an acetyl shifting from position 4 to 5 and a benzoyl from C-2 to C-20. In addition, the oxygen substituent at C-5 has epimerized. The structure of compound **9** (Scheme 2 and Table 3) was rigorously characterized by detailed NMR (HMQC, HMBC and NOESY analysis) and high resolution mass spectral data. The electrospray mass spectra was used in the negative mode.

Table 3

Proton and Carbon-13 NMR Data for compound **9**

Position	δ ^{1}H ppm	M[a]	J (Hz)	δ ^{13}C[b] ppm	Position	δ ^{1}H ppm	M[a]	J (Hz)	δ ^{13}C[b] ppm
1	--			**68.0**	14a	2.12	dd	13.9;7.1	35.8
2	4.46	o.m			14b	1.88	o.m		
OH-2	4.18		10.9		15	--			**77.8**
3	2.50	d	6.6	43.2	16	1.17	s		28.2
4	--			**76.8**	17	1.48	s		27.3
5	5.34	t	2.9	71.0	18	1.88	d	0.8	10.9
6	1.95-1.89	m		31.7	19	1.36	s		14.4
7	4.13	br.m		68.4	20a	5.02	d	12.7	65.2
OH-7	3.54	d	1.0		20b	4.67	d	11.7	
8	--			**42.3**	Ac	2.15	s		20.5; 171.9
9	4.16	o.d	10.6	81.0		2.04	s		20.8; 170.8
10	4.43	o.m		68.7	Bz				165.9
OH-10	3.60	d	9.9		o	8.06	d	8.3	129.7
11/12	--			**141.6**	m	7.47	t	7.9	128.6
12/11	--			**140.9**	p	7.58	t	7.5	133.6
13	5.60	t	6.9	79.8	OH-9	4.61	s		
					OH-4	3.35	s		
					OH-1	1.98	s		

[a] M: multiplicity; o:overlap; s:singlet; d: doublet; t:triplet; br.m: broad multiplet

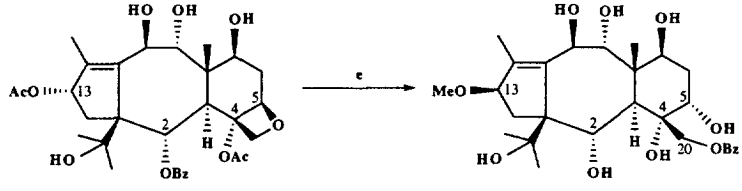
[b] The ^{13}C chemical shifts have been extracted from the HMQC experiment (±0.2 ppm). The numbers in bold character represent quaternary carbons; their shifts have been obtained fromthe HMBC experiment (±0.2ppm)

The ^{1}H and ^{13}C NMR spectral analysis showed the presence of the 11(15->1)-*abeo*-taxane structure with four C-methyls (1.17, 1.36, 1.48, 1.88), a benzoyl (8.06, 7.47, 7.58), two acetyls (2.15, 2.04), six free hydroxyls (4.61, 4.18, 3.60, 3.54, 3.35, 1.98) which also showed that oxetane ring had opened in compound **9** (also evident from absence of AB quartet for H-20 protons). The H-5 showed relatively small (2.9 Hz) coupling as compared to large (8.5 Hz) coupling observed in case of compounds **3**, **7** and **8**, indicating H-5 being equatorially oriented. This led to the result that C_5-OH epimerisation had occurred during the opening of oxetane ring. The carbon

framework of **9** was assigned by detailed analysis of HMBC data, and stereochemical assignments were made with help from NOESY experiments. The two most important features of the structure of **9** are an α-acetyl on C-5 and a benzoyl group on C-20 (Table 3). The α-acetyl on C-5 can be explained by a backside displacement which proceded with inversion at C-5 to provide a bridge hemiacetal intermediate of compound 9. The benzoyl shift was confirmed by interlocking evidence including HMBC correlation of benzoyl carbonyl carbon (165.9) with H-20a (5.02) and H-20b (4.67). Some important NOEs included a strong interaction between Me-16 and H-13 which showed their β-*cis* relationship. Me-19 showed very strong NOE with H-20b indicating this proton must be *cis* to Me-19. The Me-17 showed interaction with H-2 (4.46), H-14a (2.12), 1-OH (1.98) and Me-16 (1.17) confirming that 15-*gem*-dimethyls were above the plane.

Benzoyl shifts

In order to understand the opening of the oxetane as well as the unusual benzoyl shift, we decided to investigate the intermediacy of compound **8**. We found that after 48 hours in acidic conditions (*p*-TSA in methanol) only one major compound is obtained : taxane **11**. Purification of this compound and detailed NMR (Table 4) and mass spectral analysis rigorously confirmed that the structure was 20β-benzoyl-13β-methoxy-2α,4α,5α,7β,9α,10β,15-heptahydroxy-11(12)-ene-11(15->1)-*abeo*-taxane (**11**, Scheme 3).



8 **11**

Scheme 3. Opening of the oxetane of the *abeo*-taxane **8** is coupled with epimerisation at C-5 and an unusual benzoyl shift from the oxygen at C-2 to the one at C-20 to give *abeo*-taxane **11**. The conditions of the reaction (e) are the following: *p*-TSA H_2O (3 eq.), MeOH, RT, 48hrs.

The NMR data of taxane **11** shows that as in the case of taxane **9**, H-7 is axial and H-5 equatorial. Indeed H-5 has a relatively small coupling (2.7 Hz) indicating an equatorial orientation. The NOE between H-20 and Me-19 indicate a cis relationship. The stereochemistry of H-9 is the same as in taxane **2** : H-9 has NOE with H-2 and Me-19 and is therefore α. The structure is very similar to compound **9** except that at position 5 there is a hydroxyl group instead of an acetyl and at C-13 the α-acetyl has been replaced by a β-methoxy-group. Both compounds show a benzoyl intramolecular migration from position C-2 to C-20 and epimerization at C-5. We could envision the opening of the oxetane via a rear attack of the acyl at C-4 being stabilized by a hemiacetal. The released primary alcohol at C-20 picks up the benzoyl from position 2. These seemingly unusual benzoyl shifts can be easily rationalized by the bent U-shape[8] of the taxane skeleton. Indeed, even without the side chain taxanes have a slight U-shape which can explain these benzoyl transfers.

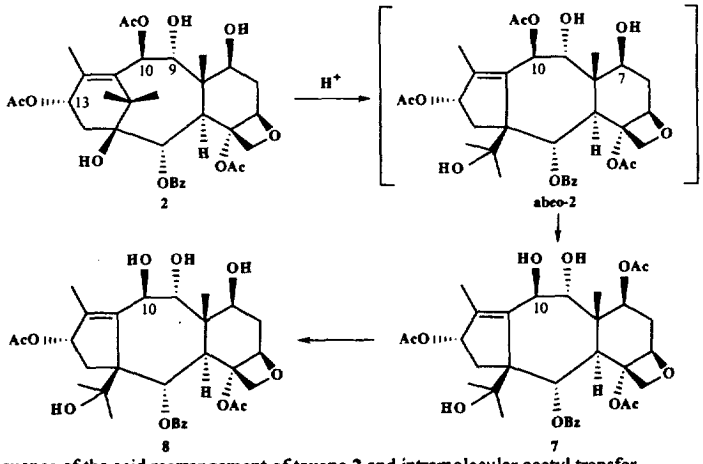
Table 4. Proton and Carbon-13 for compound **11**

Position	δ ^{1}H ppm	M[a]	J (Hz)	δ ^{13}C ppm	Position	δ ^{1}H ppm	M[a]	J (Hz)	δ ^{13}C ppm
1	--			**77.4**	15	--			**68.1**
2	4.56	o.t	8.0	68.9	16	1.12	s		28.0
OH-2	3.78	br.d	7.6	--	17	1.43	s		27.0
3	2.58	d	7.3	43.1	18	1.88	s		11.6
4	--			**76.2**	19	1.33	s		14.1
OH-4	4.38	s		--	20a	5.08	d	12.2	66.1
5	3.94	t	2.7	69.2	20b	4.53	o.d	12.7	
6a	2.10	br.ddd	14.9;4.6;3.4	33.1	OMe	3.29	s		55.4
6b	1.85	o.m			C=O				**166.5**
7	4.19	dd	11.2;4.4	68.6	Bz				
8	--			**42.8**	C2,6	8.00	d	7.3	129.6
9	4.06	d	10.0	80.4	C3,5	7.15	d	7.6	128.6
10	4.48	br.d	~10	68.9	C4	7.58	t	7.3	133.4
11/12	--			**145.5**	OH	3.50	br.s		
12/11	--			**138.1**		3.98	br.s		
13	4.25	t	6.8	85.5		4.14	br.s		
14a	1.97	dd	13.9;6.8	34.6		2.69	br.s		
14b	1.85	o.m				2.62	br.s		

[a] M: multiplicity; o:overlap; s:singlet; d: doublet; t:triplet; br.m: broad multiplet
[b] The ^{13}C chemical shifts have been extracted from the HMQC experiment (±0.2 ppm). The numbers in bold character represent quaternary carbons; their shifts have been obtained from the HMBC experiment (±0.2ppm)

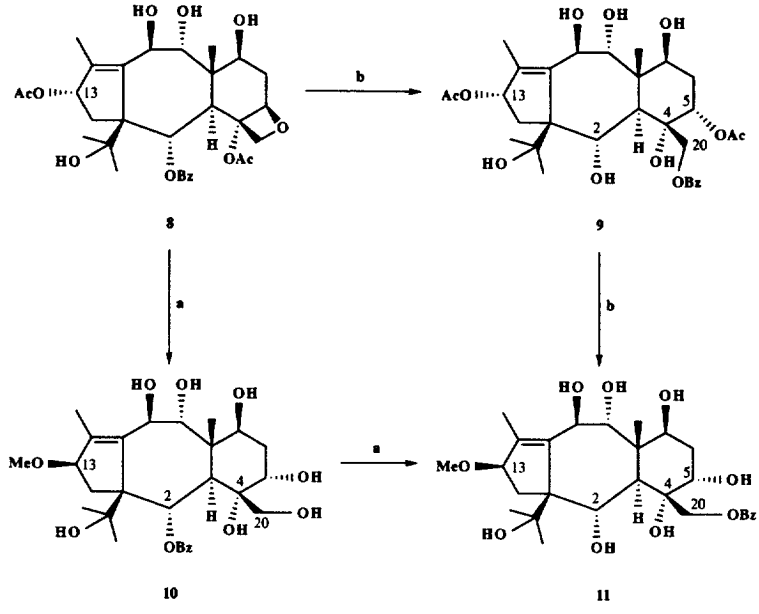
Sequence of the reactions: rearrangement, oxetane opening, methanolysis and benzoyl shifts.

In Schemes 4 and 5 we have attempted to summarize our results leading to the sequence of these successive reactions. At the moment we can only suggest plausible mechanisms but have no proof.



Scheme 4. Putative sequence of the acid rearrangement of taxane **2** and intramolecular acetyl transfer.

The formation of taxanes **7** and **8** prove conclusively that the contraction of cycle A of taxane **2** occurs prior to the opening of the oxetane. In scheme 4 we postulate that the first step is the formation of an *abeo*-**2.** We assume that the rearrangement to *abeo*-taxanes occurs prior to the intramolecular acetyl migration from C-10 to C-7 leading to taxane **7**. There is however no proof for this assumption. Next step is probably hydrolysis of the acetate giving compound **8**.



Scheme 5. Plausible pathways to explain the formation of taxane **11** from compound **8.** Pathway *a* goes through the formation of **10** whereas pathway *b* via **9.**

Compound **8** would seem to be the best precursor to **10** and **11**. In both **10** and **11** there is formation of a β-methoxyl group on C-13. The methanolysis displaces the acetate when methanol is the solvent in an SN2 type reaction, thus the β-stereochemistry of the resulting C-13-methoxy-group in taxanes **10** and **11.** In addition, all three compounds **9**, **10** and **11** have an α-hydroxylated moiety. In compound **9**, it is an acetyl obtained by the backside opening of the oxetane by the acetyl at position 4 leading to a bridged hemiacetal intermediate. In compounds **10** and **11**, the α-stereochemistry of the hydroxyl at C-5 probably goes via the same hemiacetal but here the acetyl is hydrolyzed. The conversion of compound **8** to **11** has two plausible pathways which are outlined in Scheme 5. One possibility is outlined by route a and involves formation of compound **10** followed by a benzoyl shift from C-2 to C-20 to produce compound **11**. An alternative pathway (route *b*) would be: opening of the oxetane by a backside attack via an hemiacetal intermediate to obtain the 5α-acetyl. In addition, a benzoyl shift from C-2 to C-20 will give taxane **9.** Compound **11** could then be obtained by a deacetylation at C-5 and methoxylation at C-13. We have no idea of the sequence of the reactions. We were surprised to obtain compound **11** as a major product from the reaction of purified **8**. We thought **9** will be obtained. Despite the mechanistic

possibility that compound **10** could give **11** (pathway a) we would be surprised since **10** was obtained in 72 hours reaction whereas **11** from a shorter time (48 hours). The formation of compound **10** or **11** via path a or b leading to no-benzoyl shift or with shift might depend perhaps on the half life of the hemiacetal at C4-C5 and on the group at C-13 and its stereochemistry. Indeed, in taxanes the U-shape of the molecules can explain the influence of an otherwise remote substituent. The α-acetyl or a β-methoxyl group at C-13 could therefore have an impact on the products of the reaction. Therefore there are still puzzling questions as to the sequence of the reactions and the mechanism of these unusual benzoyl shifts.

Isolation and purification of wallifoliol (12) from Taxus canadensis needles.

Rearranged products also occur in nature. Indeed, since 1993, a dozen 11(15->1)-*abeo*-taxanes have been reported in a few yew species. [9a,b] We have isolated from the needles of the Canadian yew a minor metabolite which has both cycle A and B contracted (Fig.3, Table 5).

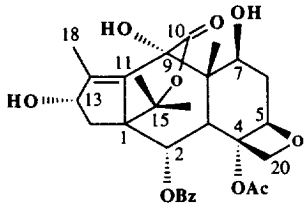
Table 5. Proton and Carbon-13 NMR Data for compound **12.**

Position	δ ^{1}H ppm	M[a]	J (Hz)	δ ^{13}C[b] ppm	Position	δ ^{1}H ppm	M[a]	J (Hz)	δ ^{13}C[b] ppm
1	--			60.1	15	--			90.4
2	5.81	d	12.0	68.1	16	1.22	s		24.6
3	2.80	dd	12.0;1.0	43.0	17	1.35	s		22.3
4	--			80.4	18	2.08	d	0.7	10.6
5	4.83	d	7.6	84.1	19	1.68	s		9.7
6	2.76	td	15.9;8.3;8.3	37.2	20a	4.65	d	8.4	73.9
	1.84	dd	15.9;8.1		20b	4.24	d	8.4	
7	4.33	td	8.0;8.0;2.4	71.0	Ac	1.74	s		21.1;169.9
8	--			48.4	OH-9	4.46	s		
9	--			84.9	OH-7	4.13	d	2.7	
10	--			*(174.6)*	Bz -C=O				164.7
11	--			139.8	C4	7.62	t		133.6
12	--			131.2	C2,6	7.98	d		129.5
13	4.56	br.t	6.8	79.5	C3,5	7.47	t		128.6
14a	2.27	dd	14.9;7.1	36.9	C1				129.7
14b	2.13	o							

[a] M: multiplicity; o:overlap; s:singlet; d: doublet; t:triplet; br.m: broad multiplet

[b] The ^{13}C chemical shifts have been extracted from the HMQC experiment (±0.2 ppm). The numbers in bold character represent quaternary carbons; their shifts have been obtained fromthe HMBC experiment (±0.2ppm)

This compound has been found in *T. canadensis* needles for the first time. The same compound with the same spectroscopic properties was previously isolated from *Taxus wallichiana* and named wallifoliol.[12]



12 Wallifoliol

Fig. 3. Wallifoliol (**12**) isolated from the needles of *Taxus canadensis*

ACKNOWLEDGMENTS

We wish to thank the Natural Sciences and Engineering Research Council of Canada and the Canadian Breast Cancer Research for support of this work via operating grants to Lolita O. Zamir. BioChem Pharma and the Fondation Armand-Frappier are acknowledged for a post-doctoral fellowship to Gaétan Caron as are the Ranbaxy Research Laboratories for granting a sabbatical leave to Sarala Balachandran

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(*Received in USA* 23 *June* 1997; *accepted* 9 *September* 1997)