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Rearrangement of the major taxane from *Taxus canadensis.*

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Abstract: The rearrangement of the major taxane 9-dihydro-13-acetyl-baccatin III (**1**) to new *abeo*-taxanes (**2,4-6**) has been studied. A sequence of reactions has been inferred. Their structures were determined by spectroscopic techniques.
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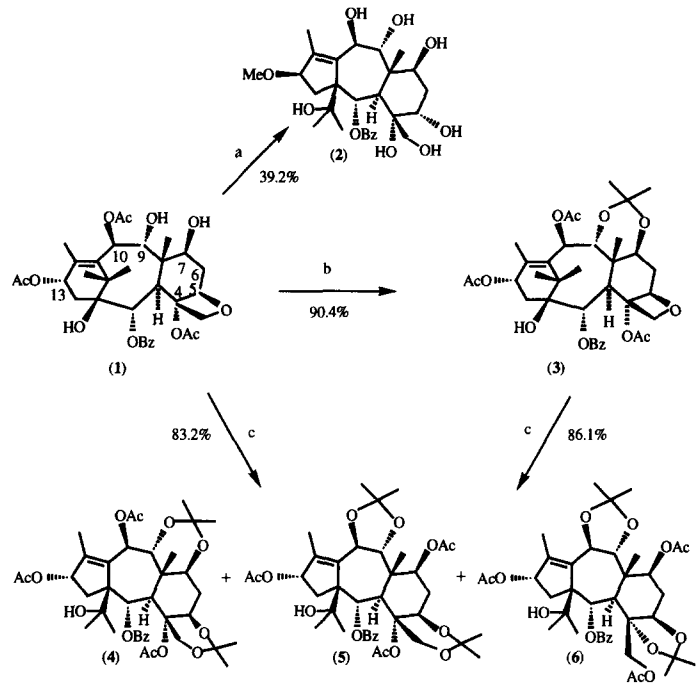
Paclitaxel, the novel diterpene natural product considered as one of the most promising drugs in cancer chemotherapy has attracted much attention in both chemical [1] and biochemical [2] societies. The unusual anticancer activity, [3] unique mode of action, [4] semi- and total syntheses [1,5] of paclitaxel are among the key discoveries. Extensive chemical studies of different *Taxus* species have led to the isolation of a large number of taxoids. [6] Since 1993, a dozen 11(15->1)-*abeo*-taxanes have been reported in a few yew species. [7a,b] Brevifoliol, which was isolated in 1991 from *Taxus brevifolia*, is also an *abeo*-taxane as was shown by the revised structure. [7c] The conversion of paclitaxel and 10-deacetylbaccatin III into *abeo*-taxanes has been successfully achieved. [6,7a] It is interesting to note that rearranged paclitaxel retained activity in the microtubule assay. [6] The study of *Taxus canadensis* [8-11] led to the isolation of a major taxane 9-dihydro-13-acetyl-baccatin III (**1**) which is five times more abundant than paclitaxel. [9,12] In this communication, we investigate the acid catalyzed rearrangement of **1** into new *abeo*-taxanes. [7d,e]

Reaction of **1** in acidic conditions (*p*-TSA in methanol, 72h) led to the *abeo*-taxane (**2**) (Scheme1) in which the oxetane has been opened. Deacetylations have occurred at positions C-4, C-10 and C-13 and the C-13 was β-methoxylated. [13] Interestingly, when this reaction was stopped after 24h two major compounds (1:1) were obtained. They both had a rearranged A-ring and an *intact* oxetane ring but differed in the positions of the acetates. Therefore, these results suggest that the rearrangement of **1** to *abeo*-taxanes precedes the opening of the oxetane. This is in agreement with the reported conversion of 10-deacetylbaccatin III and paclitaxel into *abeo*-taxanes. [6,7a] Since acidic methanol leads to extensive acetyl ester methanolysis and low yields, we decided to switch to an aprotic solvent. In addition, 2,2-dimethoxypropene (DMP) was used to trap products from the oxetane ring opening. Hence, reaction of **1** with DMP and *p*-TSA in acetone for one hour at room temperature gave the acetonide (**3**) [14] in 90.4% yield (Scheme 1) as a single product. On the other hand, when the reaction

Scheme 1.



(a) TSA (3 eq.), MeOH, R. T., 72 hrs.; (b) TSA (3 eq.), DMP (130 eq.), Acetone, R. T., 1 hr.; (c) TSA (3 eq.), DMP (130 eq.), Acetone, R. T., 72 hrs.

was carried out under the same conditions for 72 hours, compound (**3**) (R_f=0.64, ethyl acetate / hexane 7:3) was not detected in thin layer chromatography and only one new less polar spot (R_f=0.72 ethyl acetate / hexane 7:3) was observed. The ^{1}H-NMR study revealed that it consisted mainly of three *abeo*-taxanes. Separation on preparative HPLC and flash chromatography (silica gel) yielded *abeo*-taxanes (**4**) (23.0%), (**5**) (20.6%) and (**6**) (12.8%) (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 751.33060, confirming that they were isomers. Extensive NMR studies [15] on **4**, **5** and **6** clearly established their structures as shown in scheme 1. 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 (**3**) 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**).[6,16]

In summary, we demonstrated that *abeo*-taxanes (**2, 4-6**) can easily be formed from acid catalyzed rearrangement of **1**. The sequence of the reactions seems to be : i) protection of positions 7 and 9 (if DMP is used); ii) contraction of the A-ring and iii) opening of the oxetane.

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13. (**2**): FAB-MS: M^+Na: 559.25195; $C_{28}H_{40}O_{10}Na$ requires 559.25192; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 7.3 Hz, 2H), 7.59 (t, J = 7.3 Hz, 1H), 7.47 (t, J = 7.8 Hz, 2H), 5.99 (d, J = 7.3 Hz, 1H, H-2), 4.59 (br d, J = 8.3 Hz, 1H, H-10), 4.33 (t, J = 6.8 Hz, 1H, H-13), 4.25 (d, J = 10.3 Hz, 1H, H-9), 4.19 (br d, J = 6.3 Hz, 1H, H-7), 3.76 (br s, 1H, H-5), 3.49 (s, 2H, H-20), 3.41 (s, 3H, OMe), 2.93 (d, J = 6.8 Hz, 1H, H-3), 2.55 (dd, J = 7.3, 14.2 Hz, 1H, H-14a), 2.12 (dd, J = 7.1, 14.2 Hz, 1H, H-14b), 2.02 (brm, 1H, H-6a), 1.72 (brm, 1H, H-6b), 1.92 (s, 3H, Me-18), 1.32 (s, 3H, Me-19), 1.11 (s, Me-16 or 17), 1.08 (s, Me-16 or 17). Compound (**2**) was also analyzed by COSY, NOESY, HMQC and HMBC experiments.

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15. (**4**): FAB-MS: M^+Na: 751.33056; $C_{39}H_{52}O_{13}Na$ requires 751.33060; ^{1}H -NMR (500 MHz, $CDCl_3$) δ 7 .89 (d, J = 7.0 Hz, 2H), 7.51 (t, J = 7.3 Hz, 1H), 7.40 (t, J = 7.3 Hz, 2H), 6.58 (d, J = 10.0 Hz, 1H, H-10), 5.92 (d, J = 6.6 Hz, 1H, H-2), 5.59 (bt, J = 7.3 Hz, 1H, H-13), 5.21 (bt, 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), 1.55 (s, 3H, Me-19), 1.42 (s, 3H), 1.12 (s, 3H), 0.85 (s, 3H). (**5**): FAB-MS: M^+Na: 751.33056; $C_{39}H_{52}O_{13}Na$ requires 51.33060; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 8.5 Hz, 2H), 7.52 (t, J = 7.6 Hz, 1H), 7.41 (t, J = 7.6 Hz, 2H), 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), 1.13 (s, 3H), 1.12 (s, 3H), 0.87 (s, 3H). (**6**): FAB-MS: M^+Na: 751.33056; $C_{39}H_{52}O_{13}Na$ requires 751.33060; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.04 (d, J = 8.5 Hz, 2H), 7.56 (t, J = 7.6 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 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), 4.47 (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 (om, 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), 1.10 (s, 3H). All compounds (**4-6**) were completely analyzed by COSY, NOESY, HMQC and HMBC experiments.

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