Pergamon

Tetrahedron Letters, Vol. 37, No. 36, pp. 6435-6438, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01426-8

Rearrangement of the major taxane from *Taxus canadensis.*

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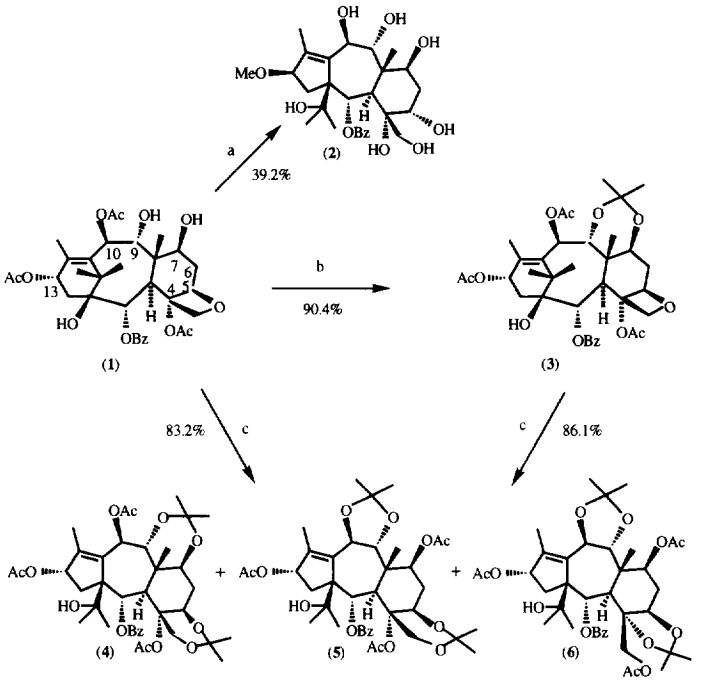
Abstract: The rearrangement of the major taxane 9-dihydro-13-acetyl-baccatin III (**1**) to new *abeo*-taxanes (**2,4-6**) has been studied. A sequence of reactions has been inferred. Their structures were determined by spectroscopic techniques.

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.

Acknowledgment: We 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 is acknowledged for a post-doctoral fellowship to Gaétan Caron.

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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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(*Received in USA* 3 *May* 1996; *revised* 15 *July* 1996; *accepted* 18 *July* 1996)