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New Rearranged Products from the Methylation of 13-Oxobaccatin III

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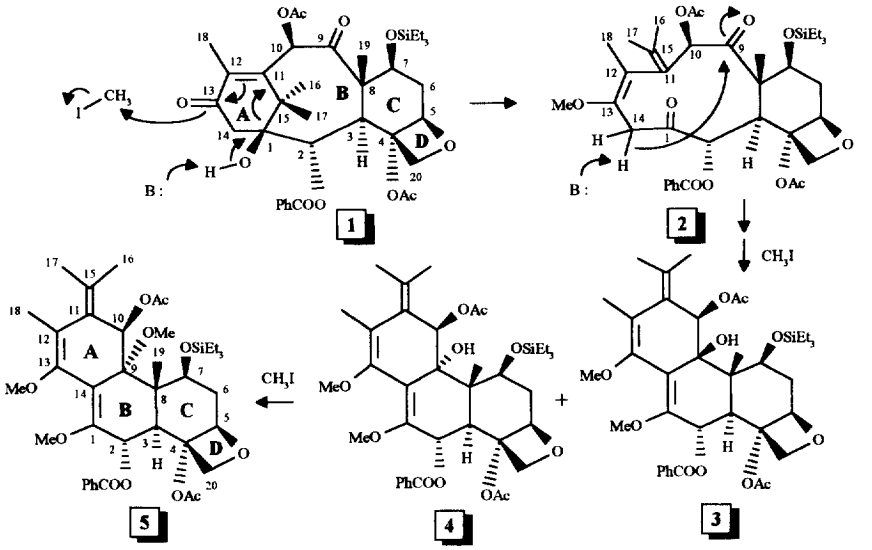
Abstract: Treatment of 7-triethylsilyl-13-oxobaccatin III (**1**) with sodium hydride and methyl iodide gave the methylated ten-membered ring compound **2** that rearranged, via intramolecular aldol condensation, to unsaturated decalin ring system (**3**, **4**, **5**). These molecules were characterized by 1D and 2D NMR tecniques. Copyright © 1996 Elsevier Science Ltd

In the course of our studies concerning the modification of the diterpenoid core of paclitaxel we were interested in the methylation of the C-1 hydroxyl. The attempts in this direction were unsuccessful. We observed instead the formation of the new rearranged compounds **2**, **3**, **4**, **5** showed in Scheme 1, characterized by the intact CD ring system of paclitaxel. Molecule **2** is a ten-membered ring diterpene similar to another rearrangement product reported in the literature,[1] and compounds **3**, **4** and **5** are new tetracyclic molecules. These products, presumably formed by the pathway showed in Scheme 1, give once more evidence of the remarkable disposition of taxoids to skeleton rearrangements.[2-8]



Scheme 1. Possible base promoted rearrangement of **1** (B = NaH)

Treatment[9] of 7-triethylsilyl-13-oxobaccatin III (**1**) with a slight excess of sodium hydride and methyl iodide produced a mixture of compounds **2**, **3** and **4**. The tricyclic compound **2** originates from the opening of ring A and methylation of the oxygen at C-13. The concomitant formation of compounds **3** and **4** can be tentatively explained as the consequence of deprotonation at the former position 14 of the baccatin nucleus followed by a transannular aldol condensation on the C-9 carbonyl. Such condensation seems to happen mainly, but not exclusively, through the β face, leading to **4** as the major product in about 30% yield, together whith **2** and **3**. When a larger excess of reactants was used,[10] compounds **3**, **4** and **5** were isolated.

The structure of these new compounds was assigned on the basis of NMR data and, above all, through ^{1}H-^{13}C heteronuclear long range correlations detected in gradient enhanced HMBC[11] experiments. Our discussion is limited to A and B rings because inspection of ^{1}H and ^{13}C NMR spectra clearly pointed out the unalterated nature of C and D rings. Analysis of gradient enhanced HMBC spectra highlighted the presence of an isopropylidene group as a common structural feature of these molecules. Two methyl groups (subsequently assigned as CH_3-16 and CH_3-17) showed mutual long range correlations in addition to those between their hydrogens and two sp^2 carbons. These latter two carbons were identified as C-15 (**2**: 141.1 ppm, **3**: 130.7 ppm, **4**: 136.3 ppm, **5**: 134.3 ppm) and C-11 (**2**: 128.2 ppm, **3**: 132.6 ppm, **4**: 129.1 ppm, **5**: 129.4 ppm) due to long-range coupling constants H-10/C-11 and H-10/C-15. Distinction of C-15 and C-11 signals was possible through H-18/C-11 HMBC cross-peak. The nature of C-15, sp^2 through all the new compounds but sp^3 in compound **1**, revealed the lack of a bond between C-15 and C-1 and therefore the alteration of the carbon skeleton.

Comparison of molecular weights suggested the presence of an additional methyl group in compound **2** (MW = 712) with respect to the starting molecule **1** (MW = 698). As a matter of fact, an extra signal attributable to a methoxy group was detected in both the ^{1}H (3.59 ppm) and ^{13}C (57.4 ppm) NMR spectra. Moreover, two resonances were detected at 146.8 ppm and 121.5 ppm in the ^{13}C spectrum showing that another double bond was present in addition to the isopropylidene unsaturation. The carbon signal at 121.5 ppm was assigned to C-12 because of a long-range coupling constant H-10/C-12 and consequently the signal at 146.8 was attributed to C-13. $C\underline{H_3}O$/C-13 cross-peak defined the substitution pattern of C-12 double bond, whose configuration was determined by $C\underline{H_3}O$/H-18 NOESY cross-peak. HMBC correlations of H-18 with C-11, C-12 and C-13 were very useful to check the carbon skeleton of this portion of the molecule and the carbonyl group positions were established by H-2/C-1, H-3/C-1,$C\underline{H_2}$-14/C-1, H-3/C-9 and H-19/C-9 cross-peaks. The absence of H-2/H-3 coupling constant due to a 90° dihedral angle and the variation of coupling constants[9] between ring C protons are attributable to conformational changes consequent to C-1/C-15 bond breaking.

Very similar NMR spectra were obtained for compounds **3**, **4** and **5** so that the same carbon skeleton could be anticipated. Mass spectra analysis revealed two methyl groups for **3** and **4** (MW = 726) and three methyl groups for **5** (MW = 740) not present in the starting material **1**. From their ^{1}H (3.1-3.8 ppm) and ^{13}C (54-62 ppm) chemical shifts these methyls were found to be oxygen bound. On the other hand, differently from **2**, NMR spectra of **3**, **4**, **5** did not show signals of CH_2-14 and of the carbonyls C-1 and C-9. These signals were replaced by two ^{13}C resonances characteristic of sp^2 carbons in an oxygen substituted double bond (**3**: 147.1, 120.1 ppm, **4**: 151.1, 119.4 ppm, **5**: 151.5, 113.5 ppm) and by the signal of an oxygen bearing sp^3 carbon (**3**: 81.6 ppm, **4**: 75.6 ppm, **5**: 82.3 ppm). The structures reported in Scheme 1 fit with these data assigning the double bond resonances to C-14 (high field) and C-1 (low field) and the signal of the oxygen bearing sp^3 carbon to C-9. These attributions were confirmed by HMBC correlations (e.g. H-19/C-9, H-2/C-1, H-10/C-9 only in **4** and **5**, H-2/C-14 only in **3**). The formation of a bond between C-14 and C-9 was proved by OH-9/C-14 cross-peak in **3** and by H-10/C-14 in **4** and **5**.

Configuration of the new chiral carbon C-9 of compounds **3**, **4** and **5** was assigned on the basis of NOE effects. In the case of compound **3**, OH-9/H-19 and H-10/H-3 NOESY cross-peaks were diagnostic to determine the β orientation of OH-9. The α orientation was suggested by OH-9/H-3 ROESY cross-peak in compound **4** (DMSO-d6 solution)[12] and by OCH_3-9/H-3 and OCH_3-9/ortho-Ph NOESY cross-peaks in compound **5** (pyridine-d5 solution).[13] Inspection of molecular stereomodels pointed out that OH-9/H-7 or OCH_3-9/H-7 distances should allow NOE build up only in 9α-OH compounds but these cross-peaks were not detected in the NOESY spectra of **4** and **5** probably due to a particular orientation of OH-9. Similarly, H-10/H-3 NOE should not be present in the same isomers and actually this cross-peak was absent the NOESY spectra of **4** and **5**.

None of these novel molecules show activity in the tubulin polymerization assay.[14] IC50 (analogs)/IC_{50} (paclitaxel) values, relative to murine melanoma B16F10, are: 70 for **2**, >140 for **4** and 56 for **5** (compound **3** was not tested).

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9. To a stirred solution of 7-triethylsilyl-13-oxobaccatin III **1** (210 mg, 0.3 mmol) in anhydrous DMF (2 mL), 55% NaH (18 mg, 0.36 mmol) was added at -15°C. After stirring for 15' at -15°C to the orange mixture MeI (31μL, 0.5 mmol) was added. The reaction mixture was stirred for 1.5 h at -15°C and poured into brine and ice and the aqueous phase was extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. The crude material was purified twice by chromatography (n-hexane-AcOEt 7:3 then CH_2Cl_2-AcOEt 92:8) to yield 28 mg (13%) of **2**,.11 mg (5%) of **3** and 70 mg (30%) of **4**.

2: FD-MS (EHC = 23 mA): 712 $(M)^{+\cdot}$ $(C_{38}\ H_{52}\ O_{11}\ Si)^{+\cdot}$ (100), 713 $(M + H)^+$ $(C_{38}\ H_{52}\ O_{11}\ Si + H)^+$ (54). ^1H NMR (600 MHz, $CDCl_3$): δ 7.95 (m, 2H, oPh), 7.59 (m, 1H, pPh), 7.46 (m, 2H, mPh), 6.95 (br s, 1H, H-10), 5.59 (s, 1H, H-2), 5.37 (br s, 1H, H-20β), 5.04 (dd, J = 7.8, 6.0Hz, 1H, H-5), 4.80 (dd, J = 10.6, 3.7 Hz, 1H, H-7), 4.71 (d, J = 8.2 Hz, 1H, H20α), 3.59 (s, 3H, OCH_3-13), 3.56 (s, 1H, H-3), 3.28 (d, J = 15.0 Hz, 1H, H-14α), 2.96 (d, J = 15.0 Hz, 1H, H-14β), 2.66 (ddd, J = 14.1, 7.8, 3.7 Hz, 1H, H-6α), 2.27 (ddd, J = 14.1, 10.6, 6.0 Hz, 1H, H-6β), 2.18 (s, 3H, H-16), 2.09 (s, 3H, CH_3CO-10), 2.03 (s, 3H, CH_3CO-4), 1.89 (s, 3H, H-18), 1.68 (s, 3H, H-17), 1.30 (br s, 3H, H-19), 0.92 (t, J = 8.0 Hz, 9H, $SiCH_2C\underline{H}_3$), 0.61 (m, 6H, $SiC\underline{H}_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.0 (C-9), 201.2 (C-1), 171.0 ($\underline{C}OCH_3$-4), 169.3 ($\underline{C}OCH_3$-10), 164.9 (Ph$\underline{C}$OO), 146.8 (C-13), 141.1 (C-15), 133.3 (C-pPh), 129.6 (C-oPh), 129.3 (C-1-Ph), 128.5 (C-mPh), 128.2 (C-11), 121.5 (C-12), 83.3 (C-5), 83.0 (C-4), 79.3 (C-20), 75.2 (C-2), 73.6 (C-10), 70.0 (C-7), 58.1 (C-8), 57.4 (OCH_3), 40.4 (C-14), 39.4 (C-3), 36.6 (C-6), 22.8 (C-17), 21.6 ($\underline{C}H_3CO$-4), 21.1 ($\underline{C}H_3CO$-10), 21.0 (C-16), 16.6 (C-18), 11.5 (C-19), 6.8 ($SiCH_2\underline{C}H_3$), 5.6 ($Si\underline{C}H_2CH_3$).

3: FD-MS (EHC = 20 mA): 726 $(M)^{+\cdot}$ $(C_{39}\ H_{54}\ O_{11}\ Si)^{+\cdot}$ (100), 727 $(M + H)^+$ $(C_{39}\ H_{54}\ O_{11}\ Si + H)^+$ (49). ^1H NMR (600 MHz, $CDCl_3$): δ 7.93 (m, 2H, oPh), 7.58 (m, 1H, pPh), 7.45 (m, 2H, mPh), 6.24 (s, 1H, H-10), 6.02 (d, J = 9.8 Hz, 1H, H-2), 4.89 (d, J = 8.7 Hz, 1H, H-20β), 4.88 (dd, J = 9.6, 4.0 Hz, 1H, H-5), 4.85 (dd, J = 11.6, 6.0 Hz, 1H, H-7), 4.47 (d, J = 8.7 Hz, 1H, H20α), 3.81 (s, 1H, OH-9), 3.72 (s, 3H, OCH_3-13), 3.49 (s, 3H, OCH_3-1), 2.52 (ddd, J = 13.4, 9.6, 6.0 Hz, 1H, H-6α), 2.40 (d, J = 9.8 Hz, 1H, H-3), 2.08 (s, 3H, CH_3CO-10), 2.02 (ddd, J = 13.4, 11.6, 4.0 Hz, 1H, H-6β), 1.93 (s, 3H, H-16), 1.86 (s, 3H, H-18), 1.71 (s, 3H, CH_3CO-4), 1.65 (s, 3H, H-17), 1.51 (s, 3H, H-19), 0.98 (t, J = 7.9 Hz, 9H, $SiCH_2C\underline{H}_3$), 0.66 (m, 6H, $SiC\underline{H}_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6 ($\underline{C}OCH_3$), 169.5 ($\underline{C}OCH_3$), 165.4 (Ph$\underline{C}$OO), 147.7 (C-13), 147.1 (C-1), 133.3 (C-pPh), 132.6 (C-11), 130.7 (C-15), 129.8 (C-1-Ph), 129.4 (C-oPh), 128.5 (C-mPh), 120.1 (C-14), 108.3 (C-12), 83.6 (C-5), 81.6 (C-9), 79.1 (C-4), 76.5 (C-20), 71.8 (C-10), 71.7 (C-7), 67.2 (C-2), 57.6 (OCH_3-1), 56.3 (OCH_3-13), 45.2 (C-3), 44.5 (C-8), 36.6 (C-6), 22.2 (C-17), 22.1 ($\underline{C}H_3CO$-10), 21.0 ($\underline{C}H_3CO$-4), 20.5 (C-16), 14.7 (C-18), 11.1 (C-19), 7.2 ($SiCH_2\underline{C}H_3$), 6.3 ($Si\underline{C}H_2CH_3$).

4: FD-MS (EHC = 22 mA): 726 $(M)^{+\cdot}$ $(C_{39}\ H_{54}\ O_{11}\ Si)^{+\cdot}$ (100), 727 $(M + H)^+$ $(C_{39}\ H_{54}\ O_{11}\ Si + H)^+$ (65). ^1H NMR (600 MHz, $CDCl_3$): δ 8.03 (m, 2H, oPh), 7.56 (m, 1H, pPh), 7.43 (m, 2H, mPh), 6.10 (s, 1H,

H-10), 6.09 (br s, 1H, H-2), 4.87 (dd, J = 9.5, 2.6 Hz, 1H, H-5), 4.86 (d, J = 8.7 Hz, 1H, H-20β), 4.84 (dd, J = 10.5, 6.9 Hz, 1H, H-7), 4.55 (d, J = 8.7 Hz, 1H, H-20α), 3.59 (s, 3H, OCH_3-1), 3.57 (d, J = 10.0 Hz, 1H, H-3), 3.53 (s, 3H, OCH_3-13), 2.66 (ddd, J = 14.4, 9.5, 6.9 Hz, 1H, H-6α), 2.40 (br s, 1H, OH-9), 2.03 (s, 3H, H-16), 1.95 (ddd, J = 14.4, 10.5, 2.6 Hz, 1H, H-6β), 1.93 (s, 3H, CH_3CO-10), 1.89 (s, 3H, H-18), 1.82 (s, 3H, H-17), 1.54 (s, 3H, H-19), 1.51 (s, 3H, CH_3CO-4), 0.98 (t, J = 7.9 Hz, 9H, $SiCH_2\underline{C}H_3$), 0.71 (m, 6H, $SiC\underline{H}_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7 ($\underline{C}OCH_3$-10), 168.5 ($\underline{C}OCH_3$-4), 165.9 (Ph$\underline{C}OO$), 151.1 (C-1), 148.0 (C-13), 136.3 (C-15), 133.1 (C-pPh), 130.2 (C-1-Ph), 129.6 (C-oPh), 129.1 (C-11), 128.4 (C-mPh), 120.7 (C-12), 119.4 (C-14), 83.1 (C-5), 80.2 (C-4), 75.6 (C-9), 75.4 (C-20), 74.6 (C-10), 69.9 (C-7), 68.5 (C-2), 61.1 (OCH_3-1), 58.3 (OCH_3-13), 47.9 (C-8), 42.4 (C-3), 38.2 (C-6), 23.3 (C-17), 21.7 (C-16), 21.0 ($\underline{C}H_3CO$-10), 21.0 ($\underline{C}H_3CO$-4), 16.1 (C-18), 11.0 (C-19), 7.1 ($SiCH_2\underline{C}H_3$), 5.7 ($Si\underline{C}H_2CH_3$).

[^1H and ^{13}C signals were assigned through the analysis of NOESY (mixing time = 1.2 s), gradient enhanced HSQC ($^1J_{HC}$ = 140 Hz) and gradient enhanced HMBC ($^1J_{HC}$ = 140 Hz and $^nJ_{HC}$ = 7 Hz) experiments].

10. To a stirred solution of 7-triethylsilyl-13-oxobaccatin III **1** (420 mg, 0.6 mmol) in anhydrous DMF (8 mL) , 55% NaH (125 mg, 2.52 mmol) was added at -15°C. After stirring for 15' at -15°C to the orange mixture MeI (233μL, 3.75 mmol) was added. The reaction mixture was stirred for 2 h at -15°C and poured into brine and ice and the aqueous phase was extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. The crude material was purified by flash chromatography (n-hexane-AcOEt 20:3) to yield 15 mg (3%) of **3**, 88 mg (20%) of **4** and 110 mg (24%) of **5**. R_f=0.24 (n-hexane-AcOEt 20:3).

5: FD-MS (EHC = 26 mA): 740 $(M)^{+\cdot}$ (C_{40} H_{56} O_{11} $Si)^{+\cdot}$ (100), 741 $(M + H)^+$ (C_{40} H_{56} O_{11} Si + H)$^+$ (85). ^1H NMR (600 MHz, $CDCl_3$): δ 8.01 (m, 2H, oPh), 7.57 (m, 1H, pPh), 7.44 (m, 2H, mPh), 6.07 (d, J = 9.4 Hz, 1H, H-2), 6.00 (s, 1H, H-10), 4.85 (dd, J = 9.6, 2.4 Hz, 1H, H-5), 4.85 (d, J = 8.3 Hz, 1H, H-20β), 4.76 (dd, J = 10.7, 7.1 Hz, 1H, H-7), 4.56 (d, J = 8.3 Hz, 1H, H20α), 3.64 (s, 3H, OCH_3-1), 3.55 (s, 3H, OCH_3-13), 3.18 (d, J = 9.4 Hz, 1H, H-3), 3.16 (s, 3H, OCH_3-9), 2.62 (ddd, J = 14.5, 9.6, 7.1 Hz, 1H, H-6α), 2.00 (s, 3H, H-16), 1.91 (s, 3H, H-18), 1.90 (s, 3H, CH_3CO-10), 1.89 (ddd, J = 14.5, 10.7, 2.4 Hz, 1H, H-6β), 1.78 (s, 3H, H-17), 1.53 (s, 3H, H-19), 1.46 (s, 3H, CH_3CO-4), 0.97 (t, J=7.9 Hz, 9H, $SiCH_2\underline{C}H_3$), 0.70 (m, 6H, $SiC\underline{H}_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6 ($\underline{C}OCH_3$-4), 168.2 ($\underline{C}OCH_3$-10), 165.7 (Ph$\underline{C}OO$), 151.5 (C-1), 148.4 (C-13), 134.3 (C-15), 133.2 (C-pPh), 130.1 (C-1-Ph), 129.5 (C-oPh), 129.4 (C-11), 128.5 (C-mPh), 124.2 (C-12), 113.5 (C-14), 83.1 (C-5), 82.3 (C-9), 80.5 (C-4), 75.5 (C-20), 74.3 (C-10), 69.9 (C-7), 68.9 (C-2), 61.3 (OCH_3-1), 58.3 (OCH_3-13), 54.4 (OCH_3-9), 50.6 (C-8), 42.2 (C-3), 38.2 (C-6), 23.3 (C-17), 21.5 (C-16), 21.1 ($\underline{C}H_3CO$-10), 21.0 ($\underline{C}H_3CO$-4), 16.5 (C-18), 11.6 (C-19), 7.1 ($SiCH_2\underline{C}H_3$), 5.6 ($Si\underline{C}H_2CH_3$). [^1H and ^{13}C signals were assigned through the analysis of NOESY (mixing time = 1.2 s), gradient enhanced HSQC ($^1J_{HC}$ = 140 Hz) and gradient enhanced HMBC ($^1J_{HC}$ = 140 Hz and $^nJ_{HC}$ = 7 Hz) experiments].

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