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Synthesis, Structure Elucidation and Biological Evaluation of C-Norpaclitaxel

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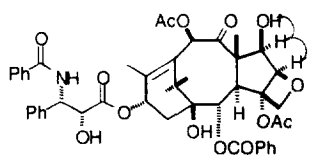
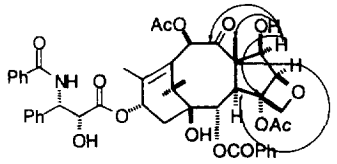
Abstract: Oxidation of 2'-TBDMS-6α-hydroxy-7-epipaclitaxel (**1**) with lead tetraacetate furnished 2'-TBDMS-C-norpaclitaxel (**2**) and the C-seco compound **3**. Deprotection of **2** with pyridinium hydrofluoride yielded C-norpaclitaxel (**4**). C-norpaclitaxel (**4**) is less effective at promoting the assembly of microtubules and less cytotoxic towards HCT116 cells than paclitaxel.

The clinical activity of the naturally-occurring antitumor agent paclitaxel (Taxol®) has spurred the preparation of numerous chemically modified paclitaxels,[1] but until recently most work has focussed on modifications of the various functional groups. Modifications to the basic taxane ring system have been relatively rare, although examples now exist of the preparation of A-nor,[2] B-nor,[3] and C-homo[4] paclitaxels. As a part of our continuing studies on the chemistry of paclitaxel,[1f] we have had a long-standing interest in modifications of ring C. We now report our preparation of C-norpaclitaxel and of a novel C-*seco*paclitaxel from the recently reported 2'- TBDMS-6α-hydroxy-7-*epi*paclitaxel (**1**).[5]

Treatment of **1** with lead tetraacetate and sodium bicarbonate in dry dichloromethane furnished 2'-TBDMS-C-*nor*paclitaxel (**2**) in 67% yield, together with a second compound **3**[6] in 11% yield. Deprotection of **2** with pyridinium hydrofluoride yielded C-norpaclitaxel (**4**)[7] in 86% yield (Scheme 1). The HRFABMS of **4** indicated it to have lost H_2CO as compared with unprotected starting material. The H,H correlations from its DQCOSY spectra and the H,C correlations from its HMBC spectra revealed the formation of a cyclic C ring (Figure 1). Acylation of **2** with acetyl chloride and 4-dimethylaminopyridine (DMAP) yielded 2'-TBDMS-6β-acetyl-C-norpaclitaxel (**5**) (Scheme 1), in which the C-6 proton was shifted downfield from 4.35 ppm to 5.44 ppm, further confirming the structure of **2**.



Key DQCOSY correlations of C-norpaclitaxel (**4**)

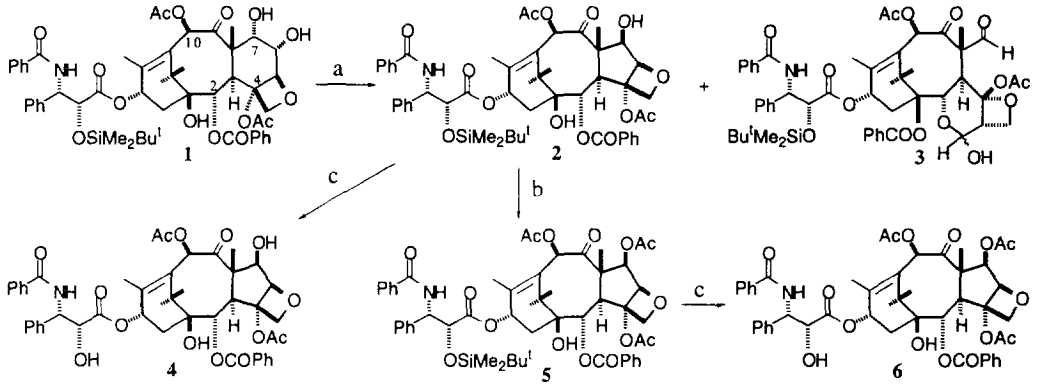


Key HMBC correlations of C-norpaclitaxel (**4**)

Figure 1

Deprotection of **5** with pyridinium hydrofluoride yielded 6β-acetyl-C-norpaclitaxel (**6**) in 90% yield (Scheme 1). The stereochemistry of the C-6 proton in **5** was determined by NOE difference spectra, which

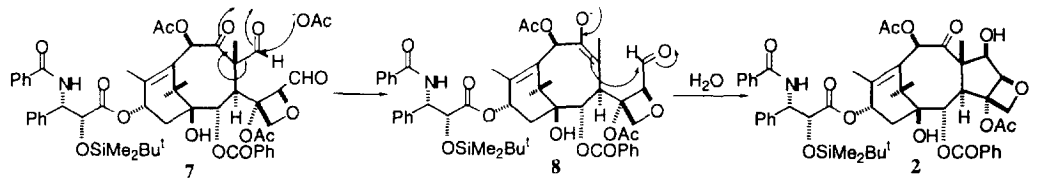
showed that the C-6 and C-5 proton signals were enhanced when the C-3 proton was irradiated, the C-6 and C-3 signals were enhanced when the C-5 proton was irradiated, and that no enhancement of the C-6 signal was observed when the C-19 methyl group was irradiated.



Reagents: (a) LTA, $NaHCO_3$, 2 hrs, 0°C; (b) CH_3COCl, DMAP, 0.5 hr, rt; (c) HF/Py, 1.5 hrs., rt

Scheme 1

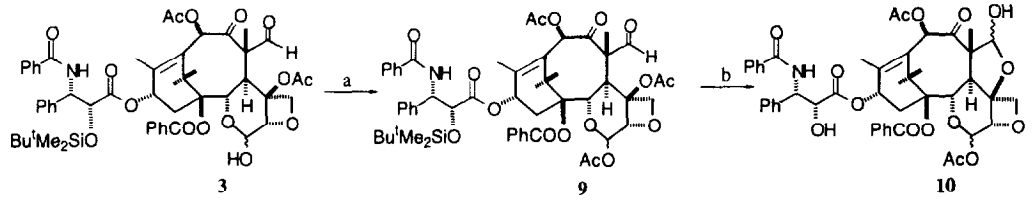
The formation of C-norpaclitaxel can be explained by normal lead tetraacetate oxidation of **1** to the dialdehyde **7**, followed by attack of an acetate ion on the electrophilic 7-carbonyl carbon to form an intermediate which then undergoes cleavage with loss of formic acetic anhydride and formation of the enolate **8**. Enolate **8** then attacks the 6-carbonyl carbon from the less hindered face (opposed to the oxetane ring) to form the 6β–hydroxy C-norpaclitaxel derivative (Scheme 2).



Scheme 2

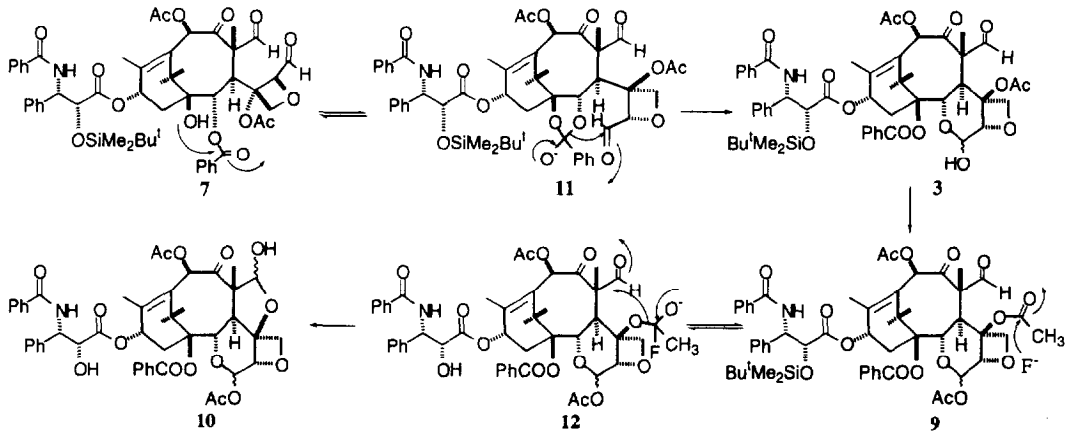
The structure of the C-seco compound **3** was established only after a full analysis of its spectroscopic data. Its composition, as deduced from its HRFABMS, indicated the loss of two protons from the starting material **1**, consistent with the formation of the dialdehyde **7**. However, the ^1H NMR spectrum of **3** showed only one aldehyde CH signal, and the aldehyde giving rise to this signal was assigned to the C-7 position from an HMBC spectrum (Figure 2). The C-2 proton correlated with a carbon resonating at 96.1 ppm and thus bearing two oxygen substituents, and the proton on this carbon (assigned from a HETCOR spectrum) correlated with the C-2 carbon in an HMBC spectrum. This evidence was consistent with the formation of a lactol between the C-6 aldehyde and the C-2 hydroxyl group (Figure 2). The downfield shift of C-1 from 79.0 ppm to 91.1 ppm and the upfield shift of C-2 from 77.8 ppm to 66.1 ppm were consistent with a benzoyl migration from C-2 to C-1. Acylation of **3** with acetic anhydride and DCC yielded the acetate **9**, in which the C-6 proton was shifted downfield from 5.38 ppm to 6.31 ppm, further confirming the structure of **3**. Deprotection of the 2'-TBDMS

group of **9** with pyridinum hydrofluoride yielded the unexpected compound **10**,[8] in which the aldehyde and one acetyl group were missing (Scheme 3). The correlations of the C-6 and C-10 protons with the carbonyl carbons of the two acetyl groups in its HMBC spectrum indicated that the 4-acetyl group had been lost. The correlation of the C-7 proton with the C-4 carbon in its HMBC spectrum indicated the formation of a lactol between the C-7 aldehyde and C-4 hydroxyl group (Figure 2). The formation of **3** and **10** can be explained by the mechanism proposed in Scheme 4.



Reagents: (a) $(CH_3CO)_2O$, DCC, PP, 8 hrs. rt, 92%; (b) HF/Py, 1.5 hr, rt, 90%

Scheme 3



Scheme 4: Mechanism of formation of **3** and **10**

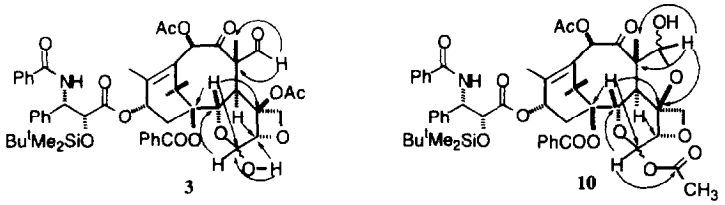


Figure 2: Key HMBC correlations of compounds **3** and **10**

The biological activities of C-norpaclitaxel **4**, its acetate **6**, and of the hemiacetal **10** were determined in a tubulin-assembly assay and (for **4**) in an HCT 116 cytotoxicity assay. Data for both assays are presented in the Table. From these data, it can be seen that C-norpaclitaxel (**4**) is significantly less cytotoxic and significantly less

effective at promoting the assembly of microtubules than paclitaxel, while compounds **6** and **10** are even less active. These results indicate that changes in the size and conformation of ring C and the attached oxetane ring make a significant difference to the activity of paclitaxel.

Table: Cytotoxicities and Effects of Paclitaxel and C-Norpaclitaxel on Tubulin Polymerization

Compound	Paclitaxel	C-Norpaclitaxel (**4**)	6-Acetyl-C-nor-paclitaxel (**6**)	Hemiacetal **10**
Cytotoxicity: HCT116 (EC_{50}, nM)	1.4	13.5	NT	NT
Tubulin Assembly: $EC_{0.01}$(μM)	6.9 ± 1.1	57 ± 26	208 ± 59	>1000

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References and Notes

1. For reviews on the chemistry and structure-activity relationships of taxol: (a) Suffness, M.; Cordell, G. A. In *The Alkaloids. Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press: New York, 1985; Vol.25, pp 3-355. (b) Blechert, S.; Guénard, D. In *The Alkaloids.Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press: San Diego, 1990; Vol. 39, pp 195-238. (c) Kingston, D. G. I. *Pharmac. Ther.* **1991**,*52*, 1-34. (d) Kingston, D. G. I.; Molinero, A. A.; Rimoldi, J. M. *Prog. Chem. Org. Nat. Prod.* **1993**,*61*, 1-188. (e) Nicolaou, K.C.; Dai, W.-M; Guy, R. K. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 15-44. (f) Kingston, D. G. I. In *Taxane Anticancer Agents: Basic Science and Current Status*; G. I. Georg; T. T. Chen; I. Ojima and D. M. Vyas, Ed.; American Chemical Society: Washington, DC, 1994; Vol. ACS Symposium Series 583; pp 203-216.
2. (a) Samaranayake, G.; Magri, N. F.; Jitrangsri, C.; Kingston, D. G. I. *J. Org. Chem.* **1991**, *56*, 5114-5119. (b) Chen, S.; Huang, S.; Wei, J.; Farina, V. *Tetrahedron* **1993**, *49*, 2805-2828.
3. Klein, L. L.; Maring, C. J.; Li, L.;Yeung, C. M.; Thomas, S. A.; Grampovnik, D. J.; Plattner, J. J.; Henry, R. F. *J. Org. Chem.* **1994**, 59, 2370-2373.
4. Bouchard, H.; Pulicani, J.-P.; Vuilhorgne, M.; Bourzat, J.-D.; Commerçon, A. *Tetrahedron Lett.* **1994**, 35, 9713-9717.
5. Liang, X.; Kingston, D. G. I.; Lin, C. M.; Hamel, E. *Tetrahedron Lett.* **1995**, 36, 2901-2904.
6. Spectral data for **3**: HRMS, *m/z* 988.4100 $(M+Li)^+$; $C_{53}H_{63}NO_{15}SiLi$ requires 988.4127: ^{1}H-NMR ($CDCl_3$, TMS) δ 9.45 (s, 1H, H-7), 7.95 (d, 2H), 7.80 (d, 2H), 7.30-7.60 (m, 6H), 7.14 (d, 1H, *J* = 8.1, NH), 6.40 (s, 1H, H-10), 6.22 (dd, 1H, *J* = 9.8, H-13), 5.66 (d, 1H, *J* = 9.2, H-3'), 5.52 (d, 1H, *J* = 8.0, H-20), 5.51 (d, 1H, *J* = 7.0, H-2), 5.38 (s, 1H, H-6), 4.85 (d, 1H, *J* = 8.0, H-20), 4.73 (d, 1H, *J* = 1.5, H-2'), 4.29 (s, 1H, H-5), 4.14 (d, 1H, *J* = 7.1, H-3), 3.37 (s, 1H, H-6-OH), 2.80-3.00 (m, 2H, H-14), 2.15 (s, 3H, $-CH_3$), 2.11 (s, 3H, $-CH_3$), 2.10 (s, 3H, $-CH_3$), 1.74 (s, 3H, $-CH_3$), 1.25 (s, 3H, $-CH_3$), 1.20 (s, 3H, $-CH_3$), 0.82 (s, 9H, $-CH_3$), -0.02 (s, 3H, $-CH_3$), -0.33 (s, 3H, $-CH_3$).
7. Spectral data for **4**: ^{1}H-NMR ($CDCl_3$, TMS) δ 8.20 (d, 2H), 7.66 (d, 2H), 7.60 (t, 1H), 7.58-7.30 (m, 5H), 6.94 (d, 1H, *J* = 9.3, NH), 6.46 (s, 1H, H-10), 6.27 (t, 1H, *J* = 8.9, H-13), 5.81 (d, 1H, *J* = 8.0, H-3'), 5.81 (d, 1H, *J* = 7.9, H-2), 5.14 (d, 1H, *J* = 4.4, H-5), 5.14 (d, 1H, *J* = 4.6, H-2'), 4.45 (d, 1H, *J* = 8.2, H-20), 4.35 (d, 1H, *J* = 7.9, H-3), 4.33 (dd, 1H, *J* = 4.3, 7.8, H-6), 4.28 (d, 1H, *J* = 8.2, H-20), 3.46 (d, 1H, *J* = 4.5, H-2'-OH), 2.53 (d, 1H, *J* = 7.8, H-6-OH), 2.43 (s, 3H, $-CH_3$), 2.21 (s, 3H, $-CH_3$), 2.12-2.20 (m, 2H, H_{14}), 1.85 (s, 3H, $-CH_3$), 1.84 (s, 3H, $-CH_3$), 1.23 (s, 3H, $-CH_3$), 1.14 (s, 3H, $-CH_3$).
8. Spectral data for **10**: ^{1}H-NMR ($CDCl_3$, TMS) δ 7.89(d, 2H), 7.82 (d, 2H), 7.56 (t, 1H), 7.50-7.30 (m, 5H), 6.95 (d, 1H, *J* = 8.1, NH), 6.49 (s, 1H, H-10), 6.20 (t, 1H, *J* = 8.1, H-13), 6.14 (s, 1H, H-6), 5.78 (d, 1H, *J* = 9.1, H-2), 5.70 (dd, 1H, *J* = 8.2, 3.4, H-3'), 5.13 (d, 1H, *J* = 3.1, H-7), 4.85 (d, 1H, *J* = 7.5, H-20), 4.72 (d, 1H, *J* = 7.4, H-20), 4.72 (d, 1H, *J* = 5.2, H-2'), 4.43 (s, 1H, H-5), 3.86 (d, 1H, *J* = 9.0, H-3), 3.68 (d, 1H, *J* = 4.5, H-2'-OH), 3.28 (s, 1H, H-7-OH), 2.65-3.00 (m, 2H, H-14), 2.19 (s, 3H, $-CH_3$), 2.13 (s, 3H, $-CH_3$), 1.80 (s, 3H, $-CH_3$), 1.43 (s, 3H, $-CH_3$), 1.26 (s, 3H, $-CH_3$), 1.25 (s, 3H, $-CH_3$).

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