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Electrochemical Reduction of Taxoids: Selective Preparation of 9-dihydro-, 10-deoxy- and 10-deacetoxy-Taxoids

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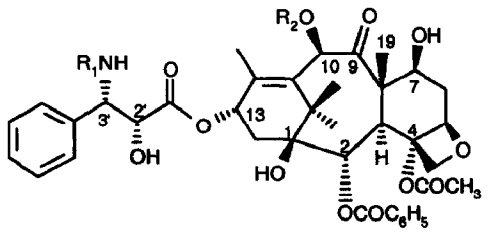
Abstract: The electrochemical reduction of docetaxel in methanol in the presence of ammonium chloride leads to 9α-dihydro-docetaxel **3** and 9β-dihydro-docetaxel **4**. Under the same conditions, the electrochemical reduction of paclitaxel gives 10-deacetoxy-paclitaxel **7**. Calcium chloride as well as magnesium and cerium chloride, and to some extent strontium and lithium chloride, favor 10-dehydroxylation in the docetaxel series. All these docetaxel analogs retain biological activity.

Semisynthetic taxoid docetaxel (Taxotere®, **1**) and natural product paclitaxel (Taxol®, **2**) are structurally unique diterpenoids exhibiting high antitumor activity[1]. Results from ongoing clinical trials for the treatment of ovarian, breast and lung cancers are very encouraging[2]. These new anticancer agents have generated growing interest because of their structural novelty, new mechanism of action[3] and, of course, their clinical activity.

As part of our research program toward new generation taxoids, we focused our efforts on the role of the hydrophilic functions located from C-7 to C-10 on the baccatin core[4]. Previous results from Chen *et al.*[5], Kingston *et al.*[6] and very recently Holton *et al.*[7] have shown that semi-synthetically prepared 10-deacetoxy-paclitaxel and 10-deoxy-docetaxel retain a high level of cytotoxicity in experimental models; reduction of the ketone at C-9 however is known to be very difficult because of its low chemical reactivity[8]. Nevertheless, Klein has recently succeeded in preparing 9α-dihydro-paclitaxel by partial synthesis from 13-acetyl-9α-dihydro-baccatin III isolated from *Taxus canadensis*[9]. This 9α-dihydro-taxoid has proved highly cytotoxic *in vitro*. These data prompted us to disclose our own results in this area.



1, R_1=tBuOCO, R_2=H (docetaxel, Taxotere®)
2, R_1=C_6H_5CO, R_2=Ac (paclitaxel, Taxol®)

The electrochemical reduction of ketones at a stirred mercury pool cathode and at controlled potential is well known and documented[10]. We felt that application of this technology to taxoids might allow regio- and stereoselective transformations without requiring any protection/deprotection strategy. We first attempted the electrolytic reduction of docetaxel **1** using ammonium chloride and ammonia in methanol as the electrolyte[11]. After preliminary cyclic voltammetry studies showed an irreversible reduction phenomena in this electrolytic medium, reduction was performed at E-1.85V vs. SCE (saturated calomel electrode) and

gave two major products (16.3F/mole used). ^{1}H-NMR analysis of these two taxoids showed that a two-electron reduction had indeed occurred at the 9-position to give 9α-dihydro-docetaxel **3** and 9β-dihydro-docetaxel **4** in 40% and 24% yield respectively[12]. This electrochemical reduction is more stereoselective when conducted on 7-epi-docetaxel **5**. Under the same conditions at a reduction potential of E-1.8V vs. SCE (5.6F/mole used), compound **5** led only to 9α-dihydro-docetaxel **6** in 63% yield.

Reduction of the ketone of paclitaxel **2**, under the same conditions as above at E-1.90V vs. SCE (6F/mole used), gave mainly one product which proved to be 10-deacetoxy-paclitaxel **7**[6] (45% yield). We subsequently found that Kabasakalian *et al.* reported an analogous deacetoxylation reaction with α-acetoxy-ketones in the steroidal series[13]. In our case, the reduction was highly regioselective since the three ester functions at C-2, C-4 and C-13 were unaffected during the electrochemical process.

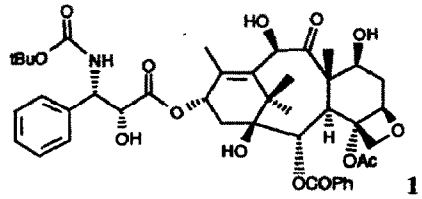
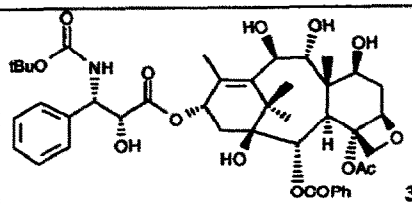
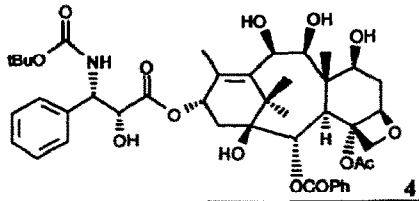
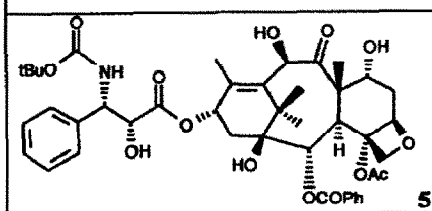
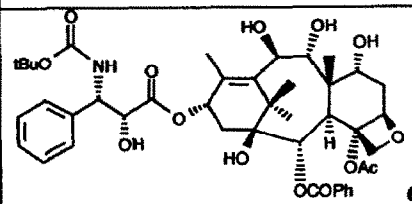
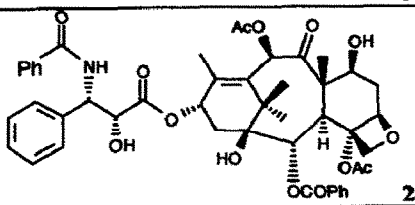
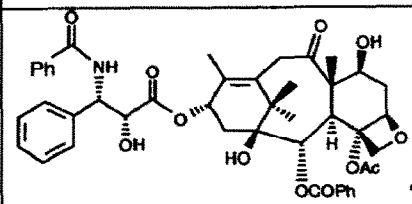
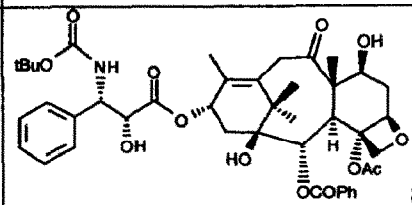
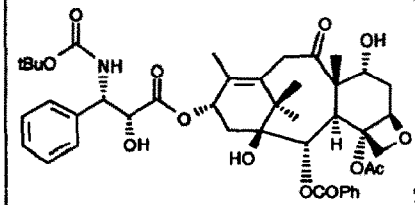
In order to achieve a dehydroxylation at C-10 in the docetaxel series, different salts able to complex the α-hydroxy-ketone at C-9,10 were added to the catholyte. The expected effect was a modification of the electronic density of the C-O alcoholic bond at C-10 able to favor the dehydroxylation process. Very recently Doxsee *et al.* described the first X-ray of calcium chloride complexed with an α-hydroxy-ketone[14]. A similar complexation of docetaxel with calcium chloride is suspected since a chemical shift of the hydrogen at C-10 is observed by ^{1}H-NMR in CD_3OH in the presence of calcium chloride. That shift is dependent on the amount of calcium salt added (δ in ppm, CD_3OH): ^{1}H-free: 5.22; ^{1}H: 5.38 in the presence of 10 equiv. of $CaCl_2$.

The electrochemical reduction of **1** in the presence of calcium chloride (0.05M) in methanol at E-1.95V vs. SCE gave, under non-optimized conditions (2.5F/mole used), two major products: 10-deoxy-docetaxel **8** and 7-epi-10-deoxy-docetaxel **9** in 15% and 20% yield respectively. Compound **9** is likely generated by a retroaldol reaction induced by an increase in basicity due to the consumption of protons at the cathode during the reduction process. The retroaldol reaction is limited when the reduction is conducted at controlled pH through the combined use of a cation-exchange type membrane and the addition of hydrochloric acid 0.2M to the anolyte. For instance reduction of 7-epi-docetaxel **5** (E-1.90V vs. SCE, 3.1F/mole used) led only to 10-dehydroxy-7-epi-docetaxel **9** in 38% isolated yield along with some 9α-dihydro-7-epi-docetaxel.

We have been able to substitute magnesium chloride as well as cerium (III) chloride, and to some extent strontium or lithium chloride, for calcium chloride thus confirming the role of a complexing salt in the dehydroxylation process. On the contrary, other cations (sodium, potassium, caesium, rubidium or barium) did not give any dehydroxylation product. Cation size (optimum 1-1.1Å) and ability to form the complex, as well as solution pH, all seem to play an important role in the regioselectivity and the yields of the reduction.

These reduced-taxoids have been biologically evaluated in *in vitro* experimental models. As previously reported for some of them (compounds **7** and **8**)[5-7], all the 9-dihydro-taxoids and 10-deoxy- or 10-deacetoxy-taxoids described here retain a high level of cytotoxicity *in vitro* against P388 leukemia cells (IC_{50} values: 0.075 μg/ml (**3**), 0.080 μg/ml (**4**), 0.13 μg/ml (**6**), 0.012 μg/ml (**7**), 0.070 μg/ml (**8**) and 0.046 μg/ml (**9**); in the same assay IC_{50} for docetaxel was 0.04 μg/ml)[15]. They are also excellent inhibitors of the disassembly of microtubules[16] (IC_{50} values: 0.4T (**3**), 0.6T (**4**), 0.6T (**6**), 0.56T (**7**), 1.15T (**8**) and 0.75T (**9**), T being the IC_{50} value for paclitaxel in the same assay; IC_{50} for docetaxel was 0.64T).

The application of selective electrochemical reduction to the taxane skeleton demonstrates the potential of this methodology in natural product chemistry. Other results will be shortly reported.

Starting material	Conditions* (E vs. SCE)	Yield**	Reduced products
 1	a (-1.85V)	40% (3) 24% (4)	 3  4
 5	a (-1.80V)	63%	 6
 2	a (-1.90V)	45%	 7
1	b (-1.95V)	15% (8) 20% (9)	 8  9
5	c (-1.90V)	38%	9

* Conditions: a) catholyte and anolyte: MeOH, NH_4Cl (0.1M), aq. 33% NH_3 (2%), H_2O (2%). b) catholyte and anolyte: MeOH, $CaCl_2$ (0.05M). c) catholyte: MeOH, $CaCl_2$ (0.05M); anolyte: MeOH, HCl (0.2M).
** Yields of isolated products.

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11. All the reductions were performed using divided cells with a cation-exchange type membrane (mercury cathode, platinum anode, SCE reference electrode). The reduction potentials were determined from polarographic curves. The theoretical number of equivalents of electrons (Faraday/mole) is 2. However an excess of current was used because of simultaneous reduction of the protic medium (hydrogen evolved at the cathode). Reactions were monitored by TLC and were stopped when degradation products are detected. Yields are not optimized since in many cases starting material was still present.
12. All new compounds exhibit IR, ^{1}H-NMR spectra and mass spectra in agreement with the structure indicated. As examples, we report herein the ^{1}H-NMR data of docetaxel derivatives.
3: foam, $[\alpha]_D^{20}$ -2 (c 0.5, MeOH), ^{1}H-NMR ($CDCl_3$, 400 MHz); δ in ppm: 1.28 (s, 3H: CH_3); 1.40 (s, 12H: $C(CH_3)_3$ and CH_3); 1.70 (s, 3H: CH_3); 1.83 (s, 3H: CH_3); 1.91 and 2.52 (2m, 1H each: CH_2 6); 2.09 and 2.37 (2dd, respectively J= 16 and 9 Hz and J= 16 and 10 Hz, 1H each: CH_2 14); 2.26 (s, 3H: $COCH_3$); 3.02 (d, J= 6.5 Hz, 1H: H 3); 4.21 and 4.31 (2d, J= 9 Hz, 1H each: CH_2 20); from 4.25 to 4.35 (m, 2H, H 9 and H 7); 4.62 (bs, 1H: H 2'); 4.91 (m, 2H: H 5 and H 10); 5.28 (bd, J= 10 Hz, 1H: H 3'); 5.68 (d, J= 10 Hz, 1H: CONH); 5.78 (d, J= 6.5 Hz, 1H: H 2); 6.10 (m, 1H: H 13); from 7.25 to 7.45 (m, 5H: C_6H_5 3'); 7.48 (t, J= 7.5 Hz, 2H: $OCOC_6H_5$ H meta); 7.62 (t, J= 7.5 Hz, 1H: $OCOC_6H_5$ H para); 8.08 (d, J= 7.5 Hz, 2H: $OCOC_6H_5$ H ortho).
4: foam, $[\alpha]_D^{20}$ -9.3 (c 0.5, MeOH), ^{1}H-NMR ($CDCl_3$, at a temperature of 323° K, 400 MHz); δ in ppm: 1.30 (s, 3H: CH_3); 1.43 (s, 12H: $C(CH_3)_3$ and CH_3); 1.70 (s, 3H: CH_3); 1.80 (s, 3H: CH_3); from 1.90 to 2.05 and 2.46 (2m, 1H each: CH_2 6); 2.05 and 2.39 (2dd, respectively J= 16 and 8.5 Hz and J= 16 and 10 Hz, 1H each: CH_2 14); 2.26 (s, 3H: $COCH_3$); 3.04 (d, J= 5.5 Hz, 1H: H 3); 4.13 (m, 1H: H 7); 4.26 and 4.25 (2d, J= 8 Hz, 1H each: CH_2 20); 4.25 (d, J= 5.5 Hz, 1H: H 9); 4.62 (bs, 1H: H 2'); 5.01 (bd, J= 6 Hz, 1H: H 5); 5.25 (d, J= 5.5 Hz, 1H: H 10): 5.29 (bb, 1H: H 3'); 5.68 (d, J= 10 Hz, 1H: CONH); 6.13 (m, 1H: H 13); 6.23 (d, J= 5.5 Hz, 1H: H 2); from 7.25 to 7.45 (m, 5H: C_6H_5 3'); 7.48 (t, J= 7.5 Hz, 2H: $OCOC_6H_5$ H meta); 7.60 (t, J= 7.5 Hz, 1H: $OCOC_6H_5$ H para); 8.10 (d, J= 7.5 Hz, 2H: $OCOC_6H_5$ H ortho).
9: foam, $[\alpha]_D^{20}$ -60 (c 0.55, MeOH), ^{1}H-NMR ($CDCl_3$, 400 MHz); δ in ppm: 1.10 (s, 3H: CH_3); 1.20 (s, 3H: CH_3); 1.36 (s, 9H: $C(CH_3)_3$); 1.62 (s, 3H: CH_3); 1.72 (s, 3H: CH_3); 1.73 (s, 1H: OH 1); from 2.15 to 2.45 (m, 4H: CH_2 14 and CH_2 6); 2.49 (s, 3H: $COCH_3$); 3.28 (bs, 1H: OH 2'); 3.43 and 4.12 (bd and d, J= 16 Hz, 1H each: CH_2 10); 3.78 (ddd, J= 12, 4 and 2.5 Hz, 1H: H 7); 4.20 (d, J= 7 Hz, 1H: H 3); 4.38 (limit AB, J=11 Hz, 2H: CH_2 20); 4.58 (d, J= 12 Hz, 1H: OH 7); 4.62 (bs, 1H: H 2'); 4.89 (dd, J= 9 and 5 Hz, 1H: H 5); 5.28 (bd, J=10 Hz, 1H: H 3'); 5.38 (d, J= 10 Hz, 1H: CONH); 5.76 (d, J= 7 Hz, 1H: H 2); 6.17 (m, 1H: H 13); from 7.30 to 7.45 (m, 5H: C_6H_5 3'); 7.52 (t, J= 7.5 Hz, 2H: $OCOC_6H_5$ H meta); 7.62 (t, J= 7.5 Hz, 1H: $OCOC_6H_5$ H para); 8.12 (d, J= 7.5 Hz, 2H: $OCOC_6H_5$ H ortho).
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