Pergamon

Tetrahedron Letters, Vol. 35, No. 52, pp. 9709-9712, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)02153-8

Preparation of 7-Modified Docetaxel Analogs Using Electrochemistry

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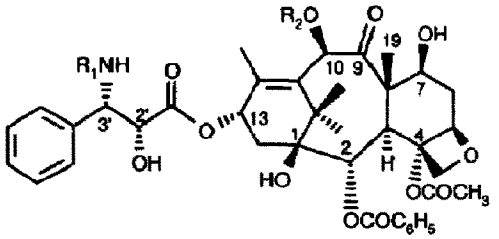
Abstract: The electrochemical reduction of 7α-iodo docetaxel at E-1.3V vs. SCE in methanol in the presence of lithium chloride and hydrochloric acid leads predominantly to 7-deoxy-docetaxel **9**. When the electroreduction is conducted at E-1.7V vs. SCE in the presence of sodium acetate and acetic acid, the cyclopropanol-containing taxoid **10** is formed in good yield. Electrochemical reduction of 7-deoxy-docetaxel at C-10 is also reported. All these docetaxel analogs retain biological activity.

Paclitaxel (Taxol®, **1**) and its semisynthetic analog docetaxel (Taxotere®, **2**) are structurally unique taxane diterpenoids (taxoids)[1] which continue to be the subject of intensive interest because of their new mechanism of action[2] and their clinical activity[3]. Paclitaxel is currently marketed in several countries for treatment of refractory ovarian cancer while docetaxel, in phase II clinical trials, exhibits encouraging results for the treatment of breast and lung cancers.



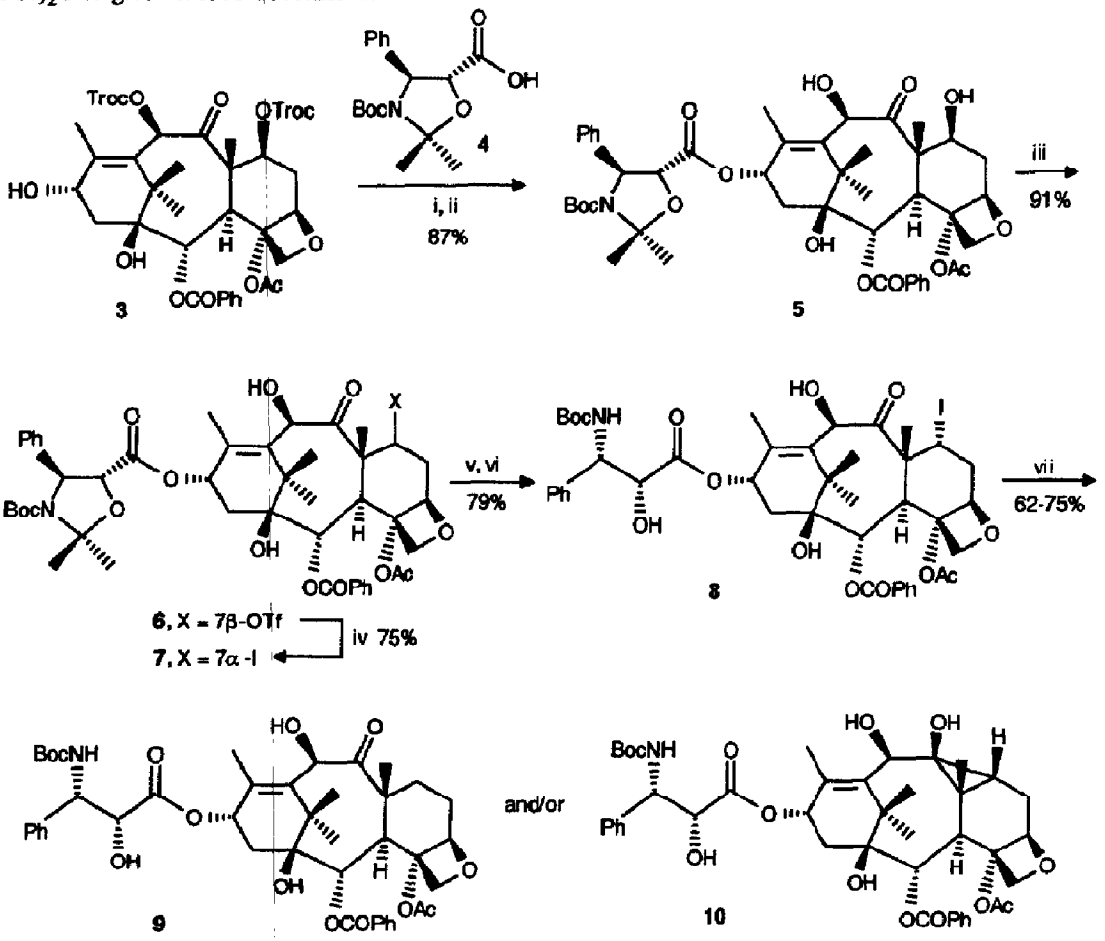
1, $R_1 = C_6H_5CO$, R_2 = Ac (paclitaxel, Taxol®)
2, R_1 = tBuOCO, R_2 = H (docetaxel, Taxotere®)

As part of our research program toward new generation taxoids we focused our efforts on the role of the hydrophilic functions of the baccatin moiety. Recently two different groups reported that 7-deoxy-paclitaxel is identical to paclitaxel in its cytotoxicity to the human colon carcinoma cell line HCT116[4]. Moreover 10-deoxy-docetaxel showed slightly better *in vitro* cytotoxicity than docetaxel against this same cell line[5] and against P388 leukemia cells[6,7] while 7,10-dideoxy-paclitaxel proved to be slightly less active than paclitaxel[4a,8]. On the basis of these data, it appears that the C-7 hydroxyl and C-10 hydroxyl (or C-10 acetoxy) groups of taxoids have only a secondary effect on the activity.

The first applications of electrochemistry to the taxoids series have recently been reported by our group[7]. In this report we described the electroreduction of docetaxel in methanol in the presence of ammonium chloride which led to 9α- and 9β-dihydro-docetaxel. Under the same conditions, the electrochemical reduction of paclitaxel gave 10-deacetoxy-paclitaxel while reduction in the presence of

calcium chloride favored 10-dehydroxylation in the docetaxel series. In this communication we wish to report complementary electrochemical results.

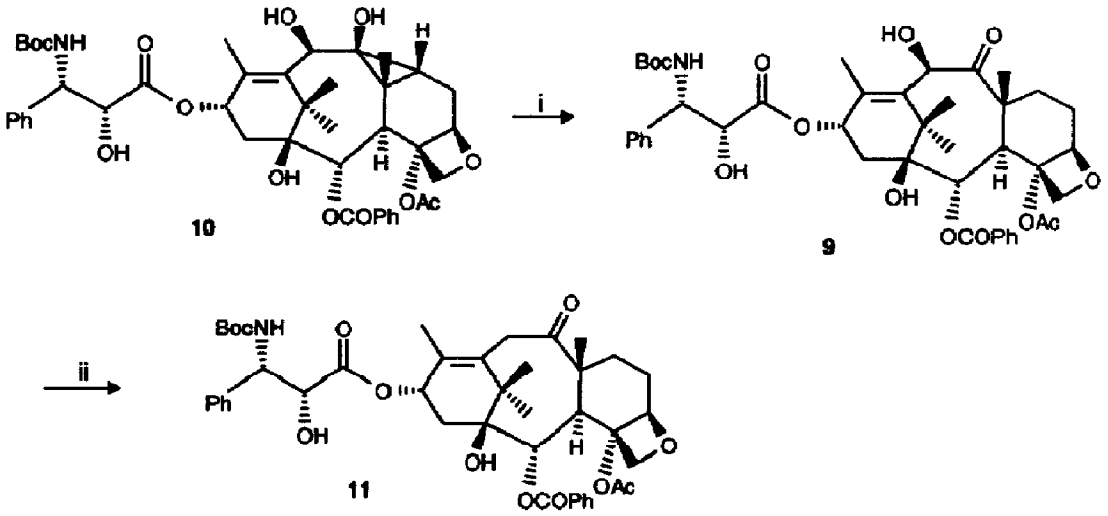
As part of further investigations on the functional modifications of taxoids, we attempted the reduction of 7α-iodo-docetaxel **8** with the aim of preparing 7-deoxy-docetaxel. The 7α-halo-compound is easily accessible as depicted below. Using standard conditions[9], esterification of the oxazolidine carboxylic acid **4** with 7,10-diTroc-baccatin III **3** followed by cleavage of the Troc (2,2,2-trichloroethoxycarbonyl) groups with zinc in acetic acid afforded the 13-O-substituted 10-deacetyl-baccatin III derivative **5**. Triflation of **5** led to the 7β-triflate **6** in good yield[10]. Nucleophilic displacement of the trifluoromethanesulfonate group with sodium iodide gave the corresponding 7α-iodo-derivative **7** again in good yield. Using a previously related sequence[9], cleavage of the oxazolidine-type protection of the phenylisoserine side-chain occurred in formic acid with concomitant removal of the Boc group. The intermediate amino derivative was reacylated with $(Boc)_2O$ to give 7α-iodo-docetaxel **8**.



Reagents: i) **3** (1 equiv.), **4** (3 equiv.), DCC (3 equiv.), DMAP (0.2 equiv.), toluene, 20°C, 1.5h. ii) Zn powder (excess), AcOH, AcOEt, 20°C, 16h. iii) Tf_2O (1.5 equiv.), CH_2Cl_2, C_5H_5N, -35°C to 0°C. iv) NaI (excess), THF, CH_3CN, 20°C. v) HCOOH, 20°C, 1h. vi) Boc_2O, CH_2Cl_2, 20°C, 64h. vii) a) formation of **9** (27%) + **10** (33%) : catholyte: MeOH, LiCl (0.1M), HCl (2.10^{-3}M); anolyte: MeOH, HCl (0.5M); Reduction potential: -1.3V vs. SCE; Q_F: 8 F/mol. b) specific formation of **10** (75%): catholyte: MeOH, AcONa (0.1M), AcOH (0.1M); anolyte: MeOH, AcONa (0.1M), AcOH (0.1M); Reduction potential: -1.7V vs. SCE; Q_F: 4.0 F/mol.

Electrochemical reduction of **8** was attempted under different conditions after initial polarographic studies showed two main reduction steps. The electrochemical reduction at a stirred mercury pool cathode and at controlled potential was performed at the first step potential, i.e. at E-1.3V vs. SCE (saturated calomel electrode), in methanol in the presence of lithium chloride and acetic acid as the electrolytic medium. The electroorganic reaction was stopped after 8F/mol of electricity was passed[11]. After work-up, the expected 7-deoxy-docetaxel **9** was obtained in 27% yield along with another reduction product. From NMR analysis, we found this new product to be the cyclopropanol-containing docetaxel analog **10**[10] (33% yield). When the reduction was conducted at the second step potential, i.e. at E-1.7V vs. SCE, and under less acidic conditions in methanol in the presence of sodium acetate and acetic acid, the cyclopropanol moiety was formed in good yield (75% yield). Thus it turns out that this cyclopropanol derivative is preferentially formed at the second reduction step under buffered conditions which might favor the intramolecular cyclization of anionic species obtained after two-electron transfer and cleavage of the carbon-halogen bond[12,13].

Ring opening of cyclopropanols under acidic conditions to give keto-alkanes is well documented[14]. We attempted such a rearrangement with compound **10**. In the presence of hydrochloric acid **10** is rearranged within 24 hours at room temperature to give 7-deoxy-docetaxel **9**[15,16].



Reagents: i) HCl 6N, AcOEt, 20°C, 24h. ii) catholyte: MeOH, $CaCl_2$ (0.05M); anolyte: MeOH, HCl (0.1M); Reduction potential: -1.9V vs. SCE; Q_F: 16.4 F/mol.

Based on our previous results[7], access to products of further electrochemical reduction of 7-deoxy-docetaxel looked conceivable. Thus the additional removal of the hydroxy group at C-10 was attempted in methanol in the presence of $CaCl_2$ as the electrolytic medium. Electroreduction at E-1.90V vs. SCE (16.4F/mole used) led to the desired 7,10-dideoxy-docetaxel **11**[4a,8] (44% yield).

All of these reduced-taxoids have been biologically evaluated in *in vitro* experimental models. As previously reported[4-6,8], compounds **9** and **11** retain high levels of cytotoxicity *in vitro* against P388 leukemia cells[17] (IC_{50}(**9**)/IC_{50}(**2**) = 0.95 and IC_{50}(**11**)/IC_{50}(**2**) = 8). Taxoid **10** is as cytotoxic as **11** with IC_{50}(**10**)/IC_{50}(**2**) = 8.25. These three analogs of docetaxel are also excellent inhibitors of the disassembly of microtubules[18] (IC_{50} values: 0.8T (**9**), 1.3T (**10**), 1T (**11**), T being the IC_{50} value for paclitaxel in the same assay; IC_{50} for docetaxel is 0.64T).

This new application of selective electrochemical reduction to the taxane skeleton reinforces the potential of this methodology in natural product chemistry. Complementary results will be reported shortly.

Acknowledgements: We thank Dr. M. Vuilhorgne and coll. for structural analyses, Drs. C. Combeau, J.F. Riou, M-C. Bissery, P. Vrignaud and F. Lavelle for biological evaluation and Dr. D. Deprez for fruitful discussions. We are also very indebted to Dr. C.J. Burns for critical reading of the manuscript.

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10. 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 the docetaxel analog **10**.
10: foam, $[\alpha]_D^{20}$ +10.6 (c 0.5, MeOH), ^{1}H-NMR (400 MHz, DMSO-d_6); δ in ppm: 0.83 (t, J=9Hz, 1H: CH); 1.12 (s, 3H: CH_3); 1.30 (s, 3H: CH_3); 1.39 (s, 9H: $C(CH_3)_3$); 1.45 (dd, J=16 and 9Hz, 1H: 1H of CH_2); 1.64 (s, 3H: CH_3); 1.70 (s, 3H: CH_3); 1.85 (d, J=9Hz, 1H: 1H of CH_2); 1.92 (s, 3H: $COCH_3$); 2.01 (ddd, J=16, 9 and 3Hz, 1H: 1H of CH_2); 2.91 (d, J=7Hz, 1H: CH); 4.12 and 4.65 (2d, J=8Hz, 1H each: CH_2); 4.31 (dd, J=8.5 and 5Hz, 1H: CH); 4.68 (s, 1H: OH); 4.85 (d, J=3Hz, 1H: CH); 4.90 (d, J=5Hz, 1H: CH); 5.03 (dd, J=10 and 5Hz, 1H: CH); 5.20 (s, 1H: OH); 5.21 (d, J=7Hz, 1H: CH); 5.62 (d, J=8.5Hz, 1H: OH); 5.84 (d, J=5Hz, 1H: OH); 5.96 (t, J=9Hz, 1H: CH); 7.20-7.35 (m, 1H: CONH); 7.25 (t, J=7.5Hz, 1H: 1H of C_6H_5); 7.29 (d, J=7.5Hz, 2H: 2H of C_6H_5); 7.36 (t, J=7.5Hz, 2H: 2H of C_6H_5); 7.54 (t, J=7.5Hz, 2H: 2H of $OCOC_6H_5$); 7.65 (t, J=7.5Hz, 1H: 1H of $OCOC_6H_5$); 7.89 (d, J=7.5Hz, 2H: 2H of $OCOC_6H_5$).
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 were detected. Yields are not optimized (starting material still present).
12. Cyclopropanation conditions can be compared to those reported with 1,3-diketones. Armand J., Boulares L., *Can J. Chem.*, **1976**, *54*, 1197-1204.
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15. This rearrangement, usually performed on mixtures of **10** and **9** obtained by electroreduction, leads under these conditions to an almost complete transformation of **10**.
16. The acidic conditions and reaction time (50 min.) used to form a mixture of **9** and **10** from **8** do not allow a significant *in situ* transformation of **10** in **9**.
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(*Received in France* 3 *October* 1994; *accepted* 28 *October* 1994)