Pergamon

Tetrahedron Letters, Vol. 35, No. 52, pp. 9717-9720, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)02155-4

Direct Access to 2-Debenzoyl Taxoids by Electrochemistry, Synthesis of 2-Modified Docetaxel Analogs

Jean-Pierre Pulicani, Daniel Bézard, Jean-Dominique Bourzat, Hervé Bouchard, Martine Zucco, Dominique Deprez and Alain Commerçon*

Rhône-Poulenc Rorer S.A.- Centre de Recherches de Vitry-Alfortville
13, Quai Jules Guesde - BP14 - 94403 Vitry-sur-Seine (France)

Abstract: A new route to semisynthetic 2-modified docetaxel analogs is described using electrochemical cleavage of the 2-benzoate as the key reaction. Subsequent reacylation at C-2 followed by sequential deprotections afforded the title analogs. Biological results of selected 2-docetaxel analogs are presented.

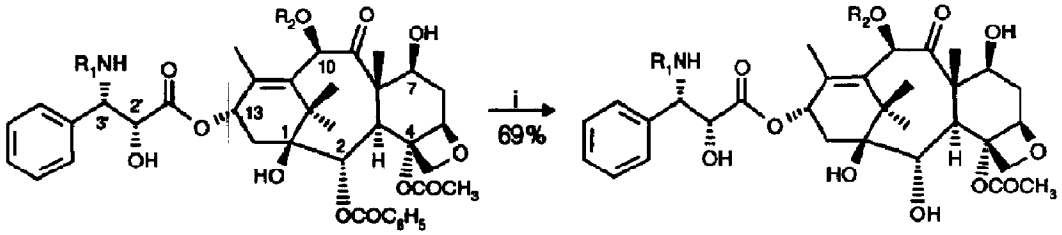
Semisynthetic docetaxel (Taxotere®) **1** and natural paclitaxel (Taxol®) **2** are two members of the taxane diterpenoids family (taxoids)[1]. These two compounds are now well-established as clinically active anticancer agents, demonstrating potent antitumor activity against different types of human cancers such as ovarian, breast and non-small-cell lung cancers[2]. The unique chemical, biochemical[3] and medicinal features of taxoids have led to extensive synthetic and medicinal studies. In the course of structure-activity relationship studies on docetaxel, we have prepared a number of new analogs modified on the baccatin moiety.

The role of the C-2 benzoate of paclitaxel has recently been examined by different groups. Chen *et al.*[4] reported the selective removal of the C-2 benzoate of 7,13-bis(triethylsilyl)-baccatin III by Red-Al. Subsequent semisynthetic work led to the preparation of weakly bioactive paclitaxel analogs with *para*-modified benzoyl groups at C-2. More recently Kingston *et al.*[5] obtained new 2-paclitaxel analogs after initial alkaline hydrolysis of 2',7-bis(triethylsilyl)-paclitaxel under phase-transfer conditions. Finally Ojima *et al.*[6] prepared 2-cyclohexanoyloxy-docetaxel by hydrogenolysis while Nicolaou *et al.*[7] synthesized 2-paclitaxel analogs by acylation of organolithium species by an intermediate 1,2-cyclic carbonate as the key reaction. Some of these 2-modified paclitaxel analogs have proven highly cytotoxic *in vitro*. These data prompted us to disclose our own results in this area.

We have recently reported the first applications of electrochemistry to effect structural modifications of taxoids[8,9,10]. In these reports we described the electroreduction of docetaxel (in methanol in the presence of ammonium chloride) at C-9 to give a mixture of 9α- and 9β-dihydro-docetaxel. Under the same conditions, the electroreduction of paclitaxel led only to 10-deacetoxy-paclitaxel while the use of calcium chloride as the supporting electrolyte allowed 10-dehydroxylation in the docetaxel series[8]. New electrochemical transformations involving the C-7 position have also been disclosed[9,10]. This communication includes complementary electrochemical results.

In cathodic reduction, the cationic moiety (R_4N^+) of the supporting electrolyte is involved in the electroorganic process[11]. Its influence may mainly result from its interaction with the active species formed at the surface of the cathode. In some cases, using a different supporting electrolyte leads to a different pattern of reaction. Thus, after electroreduction in the presence of ammonium chloride showed regioselective reduction of taxoids at C-9 or C-10[8], we used more hydrophobic ammonium salts in order to selectively reduce functional groups on other parts of the baccatin moiety.

We first attempted the direct electroreduction of docetaxel **1** using tetraethylammonium salts as the supporting electrolyte. Polarographic studies showed three reduction steps. The first wave ($E_{1/2}$-2.05V vs. SCE, saturated calomel electrode) was attributed to the one-electron reduction of the benzoate group to form a radical anion species. This wave changed to a two-electron step in the presence of a proton donor. The preparative electrochemical reduction at a stirred mercury pool cathode and at controlled potential was performed at E-1.85V vs. SCE, in acetonitrile in the presence of tetraethylammonium tetrafluoroborate and acetate buffer as the electrolytic medium. The electroorganic reaction was stopped after 4.6F/mol of electricity was passed (theory 4F/mol)[12]. After work-up, 2-debenzoyl-docetaxel **1a** was obtained in 69% yield as the sole product of taxoid reduction along with benzylalcohol formed by further electroreduction of *in situ* generated benzaldehyde.



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

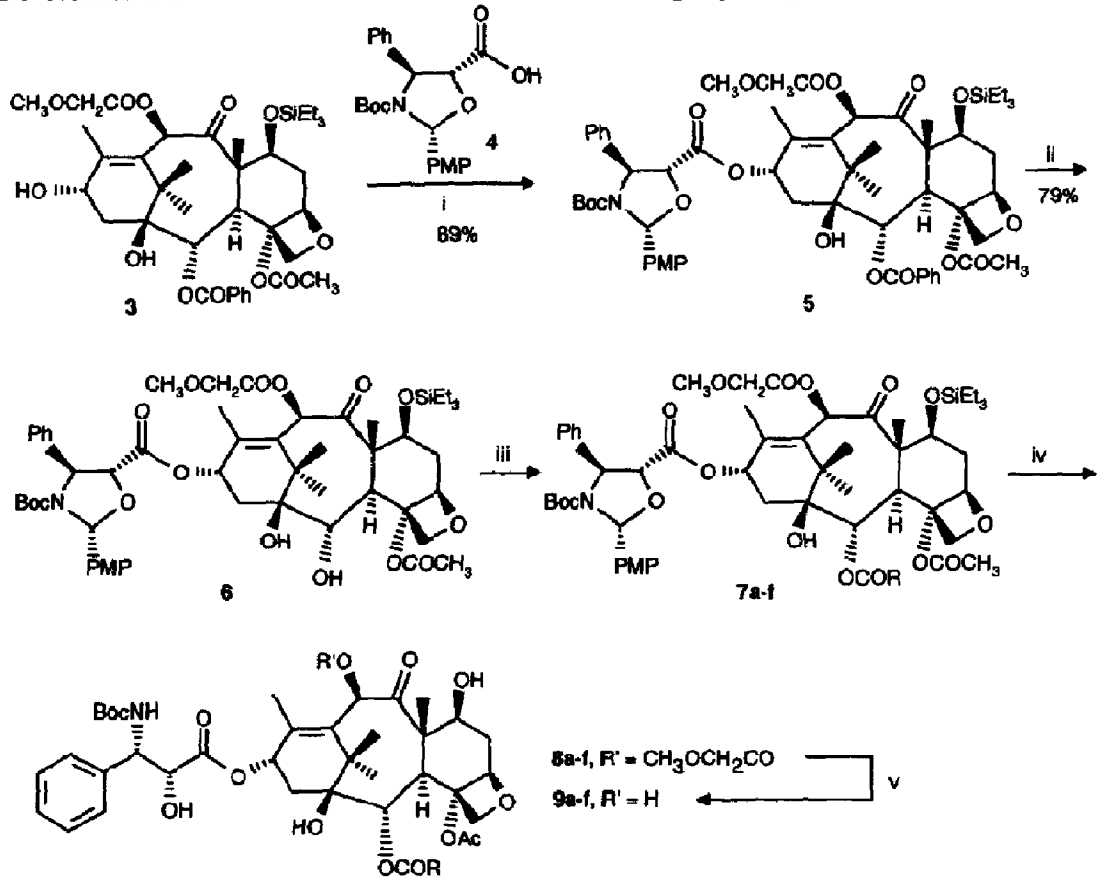
1a, R_1 = tBuOCO, R_2 = H

Reagents: i) formation of 1a from 1: catholyte: AcOH (0.05M), CH_3CN, Et_4NBF_4 (0.1M), Et_4NOAc (0.05M); anolyte: MeOH, HCl (0.1M); Reduction potential: -1.85V vs. SCE; Q_P: 4.6 F/mol.

Providing an explanation of the regioselectivity of this electroreduction is rather challenging because of the complex phenomena occuring in the electrode/solution interfacial region. Our hypothesis is that, unlike some metallic cations or ammonium chloride[8,10], hydrophobic ammonium cations prevent the activation of the α-hydroxy or α-acetoxy-ketone moiety. Tetraalkylammonium cations might favor reduction at the 2-position of the baccatin core through hydrophobic interactions between the cations adsorbed at the electrode surface and the docetaxel hydrophobic region. The presence of the benzoate at C-2 in the hydrophobic region of taxoids has been supported by NMR studies: in protic solvents docetaxel, like paclitaxel, tends to adopt a conformation which is the result of a "hydrophobic collapse"[13]. This collapse involves hydrophobic interactions between the benzene ring of the phenylisoserine side-chain, the benzoate group at C-2 and the acetate at C-4.

In order to prepare new 2-modified analogs of docetaxel, the regioselective reacylation of the hydroxy function at C-2 required the protection of the other functional groups at C-7, C-10 and on the side-chain. Thus we used the conveniently protected taxoid **5** possessing an oxazolidine-type side-chain at C-13 as substrate for electroreduction. Taxoid **5** is prepared from the baccatin III derivative **3** which is easily obtained from 10-deacetyl-baccatin III by analogy to Greene's work[14,15]. Using standard conditions[16], esterification of the oxazolidine carboxylic acid **4**, possessing a *para*-methoxy-phenyl (PMP) group at the 2-position, with the 10-deacetyl-7,10-O-diprotected-baccatin III **3** afforded compound **5** in quantitative yield. The optimized electrochemical reduction of **5** in a mixture of methanol and acetonitrile in the presence of tetraethylammonium acetate and acetate buffer at E-2.0 to -2.05V vs. SCE (5.5F/mole used) gave the 2-debenzoyl-taxoid **6** in excellent yield. Such conditions allowed us to prepare compound **6** on a 30-g scale without difficulty. Acylations of 2-hydroxy-taxoid **6** were performed by initial formation of the lithium

alkoxide followed by reaction with various acid chlorides. Cleavage of the protecting groups at C-7, C-2' and C-3' occurred under acidic conditions without removal of the Boc group[17] to give analogs **8**.



Reagents: i) **3** (1 equiv.), **4** (1.2 equiv.), DCC (1.75 equiv.), DMAP (0.2 equiv.), AcOEt, 20°C, 1.5h. ii) catholyte: $MeOH/CH_3CN$ (1/1), Et_4NBF_4 (0.1M), Et_4NOAc (0.05M), AcOH (0.05M); anolyte: MeOH, H_2SO_4 (0.2N); Reduction potential: -2.05V vs. SCE; Q_R: 5.5 F/mol. iii) BuLi (2 equiv.), THF, -78°C then RCOCl (2 equiv.), -78°C, 0.5h. iv) HCl (0.1N), EtOH, 0°C. v) MeOH, ZnI_2 (10 equiv.), 20°C, 1h.

The methoxyacetyl protecting group of the hydroxy function at C-10 was chosen because of its potentially high lability in the presence of alcohols and zinc salts[18]. In our hands this protection at C-10 has been much more rapidly cleaved than an acetyl group with zinc iodide in methanol[19,20].

Table I : Yields and biological activities of some C-2 docetaxel analogs (9a-f).

entry	Substituent R	isolated yield, %			Tubulin assay[21]	P388[22]
		7a-f	8a-f	9a-f	IC50(9)/IC50(1)	IC50(9)/IC50(1)
a	*m*-F-Ph	56	60	60	1.2	0.95
b	*m*-Cl-Ph	50	55	58	0.75	5.1
c	*m*-CF_3-Ph	54	41	30	0.7	9.3
d	*p*-F-Ph	65	69	62	0.8	12.8
e	*p*-MeO-Ph	45	62	26	5	100
f	*p*-CF_3-Ph	42	88	18	50	660

Preliminary biological evaluation of the selected compounds **9a-f** revealed cytotoxicities comparable to docetaxel against P388 leukemia cell lines (Table I). Our results confirm the negative effect of modifications

at the *para*-position and show a good correlation between cytotoxicity and inhibition of microtubules disassembly. They reinforce the hypothesis of a rather well-defined demand by the docetaxel receptor on microtubules for the C-2 ester group.

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

References and notes:

1. For recent overviews, see: a) Nicolaou K.C., Dai W.M., Guy R.K., *Angew. Chem. Int. Ed. Engl.*, **1994**, *33*, 15-44. b) Georg G.I., Ali S.E., Zygmunt J., Jayasinghe L.R., *Exp. Opin. Ther. Patents*, **1994**, *4*, 109-120. c) Kingston D.G.I., Molinero A.A., Rimoldi J.M., *Fortsch. Chem. Organ. Naturstoffe*, **1993**, *61*, 1-206.
2. a) Lavelle F., *Curr. Opin. Invest. Drugs*, **1993**, *2 (6)*, 627-635. b) Rothenberg M.L., *Curr. Opin. Invest. Drugs*, **1993**, *2 (12)*, 1269-1277. c) Pazdur R., Kudelka P.A., Kavanagh J.J., Cohen P.R., Raber M.N., *Cancer Treatment Reviews*, **1993**, *19*, 351-386.
3. Combeau C., Commerçon A., Mioskowski C., Rousseau B., Aubert F., Goeldner M., *Biochemistry*, **1994**, *33*, 6676-6683 and references cited herein.
4. Chen S-H., Farina V., Wei J-M., Long B., Fairchild C., Mamber S.W., Kadow J.F., Vyas D., Doyle T.W., *Bioorg. Med. Chem. Lett.*, **1994**, *4*, 479-482.
5. Chaudhary A.G., Gharpure M.M., Rimoldi J.M., Chordia M.D., Gunatilaka A.A.L., Kingston D G I., *J. Am. Chem. Soc.*, **1994**, *116*, 4097-4098.
6. Ojima I., Duclos O., Zucco M., Bissery M-C., Combeau C., Vrignaud P., Lavelle F., *J. Med. Chem.*, **1994**, *37*, 2602-2608.
7. Nicolaou K.C., Couladouros E.A., Nantermet P.G., Renaud J., R.K. Guy, Wrasidlo, *Angew. Chem. Int. Ed. Engl.*, **1994**, *33*, 1581-1583.
8. Pulicani J-P., Bourzat J-D., Bouchard H., Commerçon A., *Tetrahedron Lett.*, **1994**, *35*, 4999-5002
9. Pulicani J-P., Bouchard H., Bourzat J-D., Commerçon A., *Tetrahedron Lett., in press.*
10. Bouchard H., Pulicani J-P., Vuilhorgne M., Bourzat J-D., Commerçon A., *Tetrahedron Lett., in press.*
11. Shono T. in *Electroorganic synthesis*, Academic press: New York, **1991**, 11-19.
12. 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 4 including benzaldehyde reduction. However an excess of current was used because of simultaneous reduction of the protic medium (hydrogen evolved at the cathode).
13. a) Vander Velde D.G., Georg G.I., Grunewald G.L., Gunn C.W., Mitscher L.A., *J. Am. Chem. Soc.*, **1993**, *115*, 11650-11651. b) Williams H.J., Scott A.I., Dieden R.A., Swindell C.S., Chirlian L.E., Francl M.M., Heerding J.M., Krauss N.E., *Can. J. Chem.*, **1994**, *72*, 252-260. c) Dubois J., Guénard D., Guéritte-Voegelein F., Guerida N., Potier P., Gillet B., Beloeil J-C., *Tetrahedron*, **1993**, *49*, 6533-6544. d) Williams H.J., Scott A.I., Dieden R.A., Swindell C.S., Chirlian L.E., Francl M.M., Heerding J.M., Krauss N.E., *Tetrahedron*, **1993**, *49*, 6545-6560.
14. Denis J-N., Greene A.E., Guénard D., Guéritte-Voegelein F., Mangatal L., Potier P., *J. Am. Chem. Soc.*, **1988**, *110*, 5917-5919.
15. All new compounds exhibit IR, ^{1}H-NMR spectra and mass spectra in agreement with the structure indicated.
16. a) Commerçon A., Bernard F., Bézard D., Bourzat J-D., *Tetrahedron Lett.*, **1992**, *33*, 5185-5188. b) Bourzat J-D., Commerçon A., *Tetrahedron Lett.*, **1993**, *34*, 6049-6052.
17. Didier E., Fouque E., Taillepied I., Commerçon A., *Tetrahedron Lett.*, **1994**, *35*, 2349-2352.
18. The high ability of zinc^{2+} to complex methoxyacetates has been supported by theoretical calculations, Inanaga J., Kyushu University, *personal communication.*
19. Chen S-H., Farina V., Wei J-M., Long B., Fairchild C., *Tetrahedron Lett.*, **1993**, *34*, 3205-3206.
20. Yields reported in table I are unoptimized.
21. Riou J-F., Naudin A., Lavelle F., *Biochem. Biophys. Res. Commun.*, **1992**, *187*, 164-170
22. Chauvière G., Guénard D., Picot F., Sénilh V., Potier P., *C. R. Acad. Sciences, Série II*, **1981**, *293*, 501-503.

(*Received in France* 6 *October* 1994; *accepted* 28 *October* 1994)