Pergamon

Tetrahedron Letters, Vol. 35, No. 52, pp. 9713-9716, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)02154-6

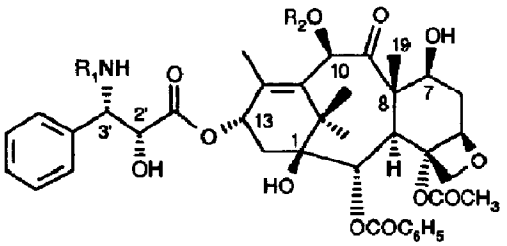
Improved access to 19-Nor-7β, 8β-Methylene-Taxoids and Formation of a 7-Membered C-Ring Analog of Docetaxel by Electrochemistry

Hervé Bouchard, Jean-Pierre Pulicani, Marc Vuilhorgne, Jean-Dominique Bourzat 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 19-nor-7β, 8β-methylene taxoids, such as compound **8**, from the 7-O-trifluoromethanesulfonyl derivative **6** is reported. Evidence for a dissociation of the triflate to form a carbocation at C-7 under the reaction conditions is presented. Electrochemical reduction of the cyclopropane taxoid **8** gives, besides the expected 10-dehydroxy-cyclopropane analog **10**, the 7-membered C-ring derivative **11**.

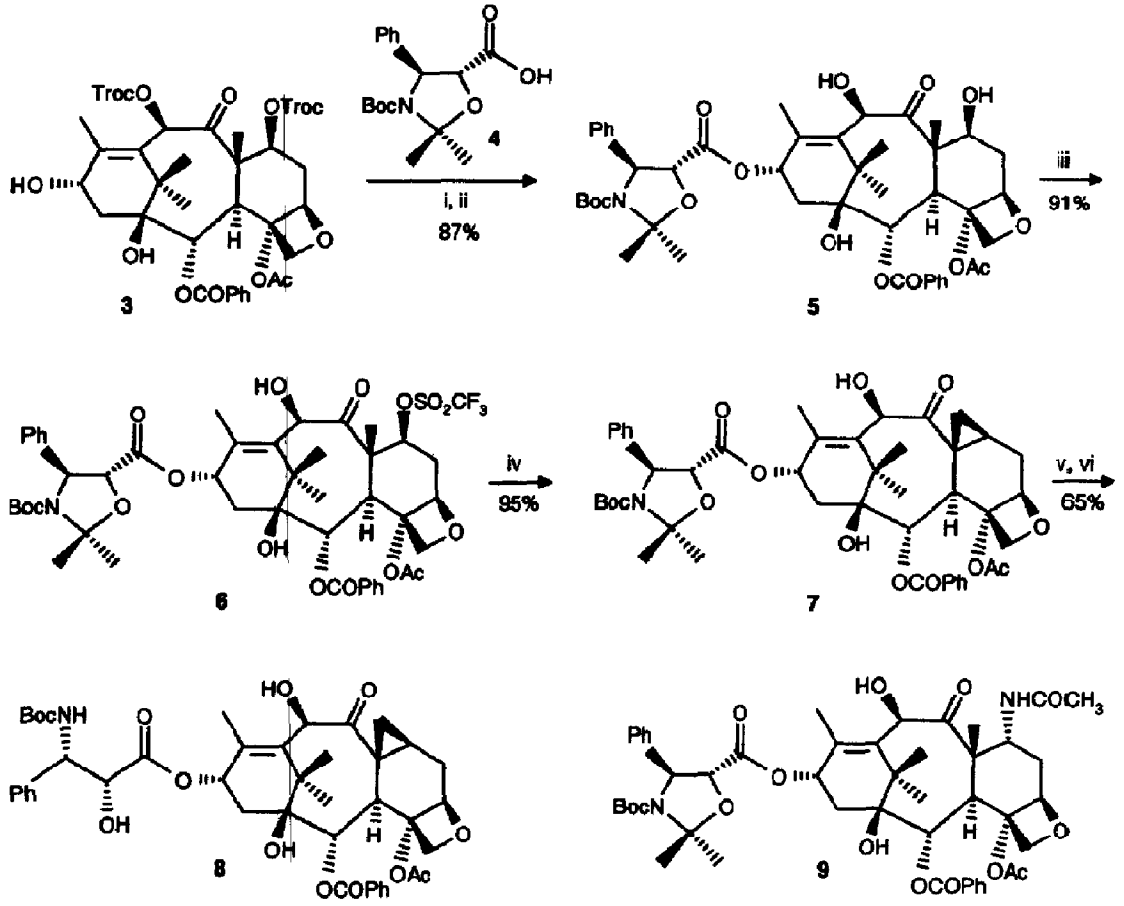
Semisynthetic docetaxel (Taxotere®) **1**, and natural paclitaxel (Taxol®) **2**, are now well-established as clinically active anticancer agents[1]. This new class of spindle poisons has generated huge interest among synthetic and medicinal chemists because of the chemical challenges posed by paclitaxel total synthesis[2], the understanding of taxoids mechanism of action at the molecular level[3] and the goal of completely defining structure-activity relationships (SAR)[4]. In connection with our own SAR studies, we investigated the role played by the different functional groups of the diterpenic moiety.



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

Like other groups, we focused our attention on modifications at C-7 and attempted to prepare new analogs of docetaxel by nucleophilic substitution of a taxoid possessing electrofugal ability at C-7. We initially planned to treat a derivative of the C-7 hydroxyl group as its triflate with different nucleophilic agents. In order to avoid undesired triflation of the phenylisoserine chain at C-13, we used a 2,2-dimethyloxazolidine-type protection[5]. Compound **5** is readily accessible by esterification of the oxazolidine carboxylic acid **4** with 7,10-O-diTroc 10-deacetylbaccatin III **3**[6], as previously reported by our group, followed by deprotection of the 2,2,2-trichloroethoxycarbonyl (Troc) groups by zinc in acetic acid under standard conditions[5]. This side-chain protected taxoid **5** was treated with one equivalent of triflic anhydride in the presence of pyridine to give the mono-triflate **6** in very good yield[7]. This triflate has proven rather stable and was tested against different nucleophiles. Thus reaction with sodium azide in THF/acetonitrile gave the complete disappearance of the starting material at reflux within 1 hour. Surprisingly enough, after work-up, the isolated reaction product was not the expected 7α-azido compound but, according to extensive NMR studies, the cyclopropane-containing

taxoid 7. Such rearranged taxoids have been reported recently by Chen *et al.*[8] who isolated a cyclopropane derivative as the by-product of the C-7 fluorination of 2'-protected paclitaxel with DAST and by Klein *et al.*[9] who identified in very low yield a cyclopropane analog during the B-ring rearrangement of a 9-dihydro baccatin III derivative with triflic anhydride. These authors assumed that the unexpected formation of the 3-membered ring involving C-7, C-8 and C-19 could arise from the trapping of a putative carbocation at C-7 by the C-8 methyl group followed by loss of a proton *via* a protonated cyclopropane intermediate.

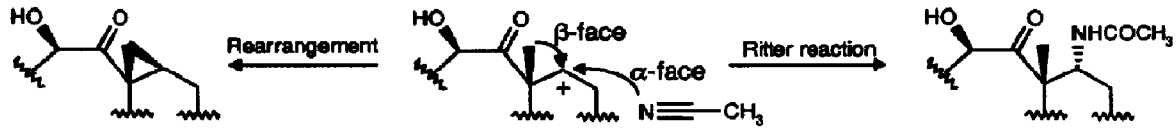


Reagents: i) **3** (1 equiv.), **4** (3 equiv.), DCC (3 equiv.), DMAP (0.2 equiv.), toluene, 20°C, 1.5h. ii) Zn powder, AcOH, AcOEt, 20°C, 16h. iii) Tf_2O (1.5 equiv.), CH_2Cl_2, C_5H_5N, -35 to 0°C. iv) NaN_3 (excess), THF, CH_3CN, reflux, 1 h. v) HCOOH, 20°C, 1 h. vi) Boc_2O, CH_2Cl_2, 20°C, 64 h.

In looking for by-products we found the 7α-acetylamino taxoid **9** formed in about 5% yield. The presence of this minor product is in agreement with the formation of a carbocationic species under the rearrangement conditions. This cation is very likely trapped by the nucleophilic attack of acetonitrile from the less hindered α-face in a Ritter-type reaction[10].

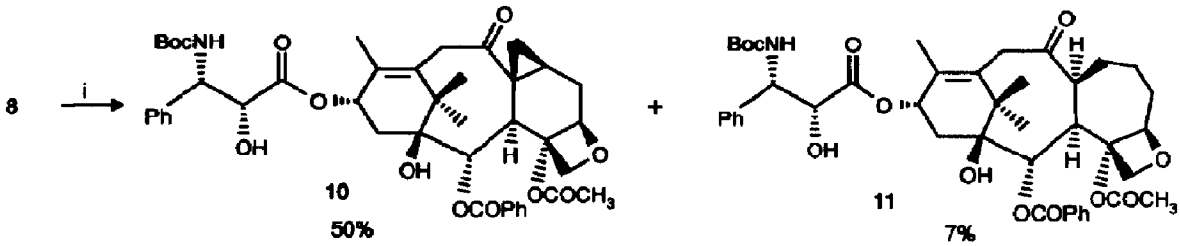
We completed the partial synthesis of the docetaxel cyclopropane analog **8** by concomitant removal of the Boc group and oxazolidine ring cleavage with formic acid followed by acylation of the intermediate 3'-

amino taxoid with Boc_2O[5]. The docetaxel analog **8** proved to be very cytotoxic in experimental models (P388 leukemia cells).



To explore further the medicinal chemistry of this cyclopropane derivative, the regioselective reduction of **8** at C-10 by electrochemistry was studied.

We recently reported the electrochemical dehydroxylation of docetaxel at C-10 in the presence of different cations such as Ca^{2+} or Ce^{3+} in the electrolyte[11]. After initial polarographic studies showed a reduction phenomenon of **8** in methanol in the presence of $CeCl_3$ as the electrolyte, the electrochemical reduction was performed using a divided cell with a cation-exchange type membrane, on a stirred mercury pool cathode and at the controlled potential of E-1.75V vs. SCE (saturated calomel electrode). The electrolysis was stopped after 4.6F/mol of electricity was passed. After work-up, the expected 10-dehydroxy cyclopropane analog **10** was obtained in 50% yield along with a minor product of further reduction. From NMR analysis, we found this minor compound to be the new C-ring-rearranged taxoid **11**[7] (7% yield). Ring opening of conjugated cyclopropane ketones by electron transfer reactions using lithium in ammonia or samarium(II) iodide as well as under irradiation conditions is well-known[12]. It has also been shown that the bond of the cyclopropane which is reductively cleaved corresponds to the bond which better overlaps with the π system of the adjacent carbonyl group (in this case the C7-C8 bond)[13]. The stereochemical configuration assigned by NMR for the carbon atom at the 8-position of the newly formed 19-nor 7β, 8β-methylene taxoid **11** is in agreement with the cleavage of the C7-C8 bond followed by protonation of the intermediate enolate from the α-face.



Conditions: i) catholyte: MeOH, $CeCl_3$ (0.033M); anolyte: MeOH, HCl (0.1M); Reduction potential: -1.75V vs. SCE; Q_F: 4.6 F/mol.

This new C-ring-rearranged taxoid was biologically evaluated in different experimental models. Although retaining strong conformational analogies with docetaxel according to preliminary molecular modelling studies[14], **11** proved to be completely inactive as an inhibitor of microtubule disassembly and displayed no cytotoxic effect against P388 leukemia cell lines thus highlighting the importance of the 6-membered C-ring system for antitumor activity.

Acknowledgements: We thank Drs. C. Combeau, J.F. Riou, M-C. Bissery, P. Vrignaud and F. Lavelle for biological evaluation and Drs. M. Zucco and A. Laoui for molecular modelling studies. We are also indebted to Dr. C.J. Burns for critical reading of the manuscript.

References and notes:

1. 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.
2. Wessjohann L., *Angew. Chem. Int. Ed. Engl.*, **1994**, *33*, 959-961 and references cited herein.
3. Combeau C., Commerçon A., Mioskowski C., Rousseau B., Aubert F., Goeldner M., *Biochemistry*, **1994**, *33*, 6676-6683 references cited herein.
4. For recent reviews on the topic, see: a) Kingston D.G.I., *Progress in the Chemistry of Organic Natural Products*, **1993**, 1-206. b) Nicolaou K.C., Dai W-M., Guy R.K., *Angew. Chem. Int. Ed. Engl.*, **1994**, *33*, 15-44. c) Georg G.I., Ali S.M., Zygmunt J., Jayasinghe L.R., *Exp. Opin. Ther. Patents*, **1994**, *4*, 109-120.
5. 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.
6. Sénilh V., Guéritte F., Guénard D., Colin M., Potier P., *C. R. Séances Acad. Sci. Paris*, (série 2), **1984**, *29*, 1039-1043.
7. 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 cyclopropane-containing and the 10-dehydroxy 7-membered C-ring analogs of docetaxel.
   8: foam, ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.23 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.34 (s, 9H, $C(CH_3)_3$), 1.35-1.50 (m, 1H, CH), 1.63 (dd, J=7.5 and 5.5Hz, 1H, 1H of CH_2), 1.73 (s, 3H, CH_3), 1.84 (s, 1H, OH), 2.11 (bd, J=17.5Hz, 1H, 1H of CH_2), 2.19 (dd, J=10.5 and 5.5Hz, 1H, 1H of CH_2), 2.25 (dd, J=16 and 9.1Hz, 1H, 1H of CH_2), 2.35-2.50 (m, 2H, two 1H of CH_2), 2.36 (s, 3H, $COCH_3$), 3.27 (m, 1H, OH), 3.43 (bd, J=17.1Hz, 1H, 1H of CH_2), 3.71 (d, J=17.1Hz, 1H, 1H of CH_2), 3.99 (d, J=7.1Hz, 1H, CH), 4.08 and 4.32 (2d, J=8.1Hz, 2H of CH_2), 4.33 (d, J=7.1Hz, 1H, CH), 4.61 (bs, 1H, CH), 4.74 (bd, J=4.5Hz, 1H, CH), 5.27 (bd, J=10.1Hz, 1H, CH), 5.37 (d, J=10.1Hz, 1H, CONH), 5.71 (d, J=7.1Hz, 1H, CH), 6.18 (bt, J=9.1Hz, 1H, CH), 7.30-7.50 (m, 5H, C_6H_5), 7.51 (t, J=7.5Hz, 2H, 1H of $OCOC_6H_5$), 7.61 (t, J=7.5Hz, 1H, 1H of $OCOC_6H_5$), 8.15 (d, J=7.5Hz, 2H, 2H of $OCOC_6H_5$).
   11: foam, ^{1}H-NMR (250 MHz, DMSO-d_6): δ 1.20 (s, 3H, CH_3), 1.25 (s, 9H, $C(CH_3)_3$), 1.30 (s, 3H, CH_3), 1.76 (s, 1H, OH), 1.85 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 2.05 (m, 1H, 1H of CH_2), 2.17 (s, 3H, $COCH_3$), 2.26 (dd, J=15 and 9Hz, 1H, 1H of CH_2), 2.34 (dd, J=15 and 9Hz, 1H, 1H of CH_2), 2.60 (m, 1H, 1H of CH_2), 3.82 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.95 (d, J=7Hz, 1H, CH), 4.14 (d, J=8Hz, 1H, 1H of CH_2), 4.30 (d, J=8Hz, 1H, 1H of CH_2), 4.62 (d, J=12Hz, 1H, 1H of CH_2), 4.90 (limit ab, 2H, CH_2), 4.90 (m, 1H, CH), 4.92 (m, 1H, CH), 4.92 (d, J=12Hz, 1H, 1H of CH_2), 5.36 (d, J=2Hz, 1H, CH), 5.63 (dd, J=11 and 7Hz, 1H, CH), 5.70 (d, J=7Hz, 1H, CH), 6.28 (s, 1H, CH), 6.34 (t, J=9Hz, 1H, CH), 6.43 (dd, J=7.5 and 1.5Hz, 1H, H(C_6H_5)), 6.51 (d, J=1.5Hz, 1H, H(C_6H_5)), 6.69 (s, 1H, CH), 7.16 (d, J=7.5Hz, 1H, H(C_6H_5)), 7.35-7.50 (m,3H, H(C_6H_5)), 7.48 (t, J=7.5Hz, 2H, H(C_6H_5)), 7.57 (d, J=7.5Hz, 2H, H(C_6H_5)), 7.63 (t, J=7.5Hz, 1H, H(C_6H_5)), 8.04 (d, J=7.5Hz, 2H, H(C_6H_5)).
8. a) Chen S-H., Huang S., Wei J., Farina V. *J. Org. Chem.* **1993**, *58*, 4520-4521. b) Chen S-H., Huang S., Farina V. *Tetrahedron Lett.*, **1994**, *35*, 41-44. c) Chen S-H., Kant J., Mamber S.W., Roth G.P., Wei J-M., Marshall D., Vyas D.M., Farina V., *Bioorg. Med. Chem. Lett.*, **1994**, *4*, 2223-2228.
9. Klein L.K., 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.
10. Krimen L.I., Cota D.J., *Org. React.*, **1969**, *17*, 213-325. We checked that 7 does not give **9** under the reaction conditions.
11. Pulicani J-P., Bourzat J-D., Bouchard H., Commerçon A., *Tetrahedron Lett.*, **1994**, *35*, 4099-5002.
12. a) Norin T., *Acta. Chem. Scand.*, **1965**, *19*, 1020-1022. b) Dauben W.G., Deviny E.J., *J. Org. Chem.*, **1966**, *31*, 3794-3798. c) Batey R.A., Motherwell W.B., *Tetrahedron Lett.*, **1991**, *32*, 6211-6214. d) Cossy J., Furet N., *Tetrahedron Lett.*, **1993**, *34*, 8107-8110.
13. Deslongchamps P. in "Stereoelectronic Effects in Organic Chemistry", Pergamon Press, N.Y., **1983**, 246-249.
14. Zucco M., Laoui A., Rhône-Poulenc Rorer, *unpublished results*.

(*Received in France* 4 *October* 1994; *accepted* 28 *October* 1994)