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A High Yield Semisynthetic Approach to 2'-epi-Taxol

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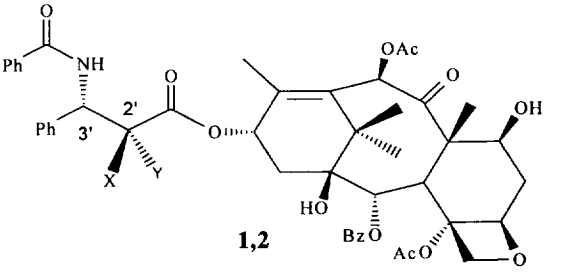
Abstract: A new 2-steps synthesis of 2'-epi-Taxol starting from natural Taxol® is described. The approach is centred on the formation of oxazoline on the side chain with concomitant inversion of the C-2' followed by acid hydrolysis. Copyright © 1996 Elsevier Science Ltd

Taxol® (Paclitaxel) **1** is a potent anticancer drug and due to its unique mode of action this molecule became rapidly one of the most important weapon against refractory advanced ovarian and breast cancer.[1] Several analogues have been synthetised in order to identify new molecules with an improved pharmacological profile and better bioavailability.[2] In this context, reference standards with a biological activity that range from nanomolar to micromolar are needed. 2'-epi-Taxol **2** is a good reference standard for biological evaluation of micromolar active taxoids in both microtubule disassembly and cytotoxicity assays because this product has the same solubility of **1**.[3]

We wish to report therein a rapid high yield synthesis of **2** starting from **1.** The (2'R,3'S) oxazoline derivative is the key intermediate of the Kingston approach to the synthesis of Taxol derivatives.[4]

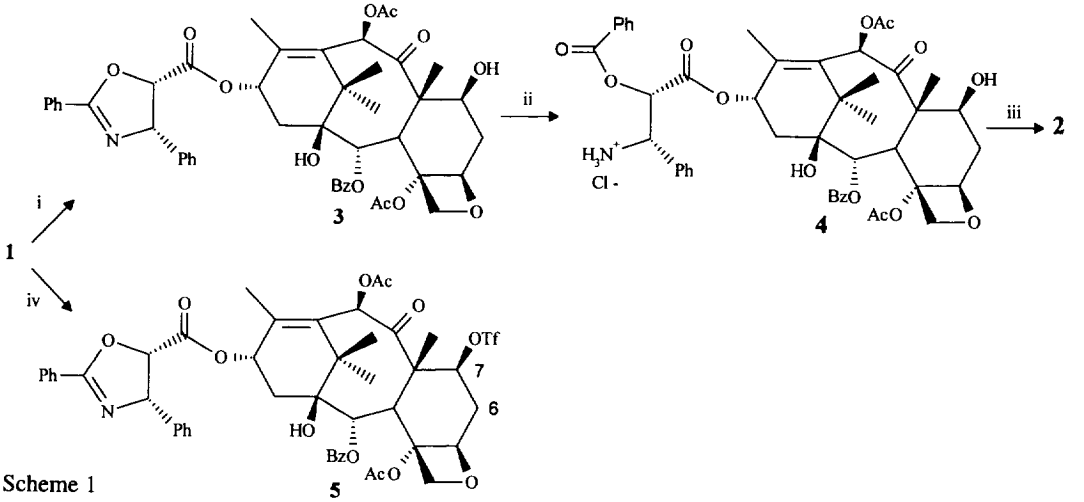
		X	Y
Taxol®	**1**	**H**	**OH**
2'epi-Taxol	**2**	**OH**	**H**



1,2

Treatment of **1** with one equivalent of trifluomethanesulfonic anhydride in CH_2Cl_2 / pyridine at -30°C→ rt affords smoothly in 4h oxazoline **3** with complete inversion at the C-2' configuration (**R→S**) in high yield (Scheme 1).[5,6] After usual work up and flash chromatography compound **3** is isolated in 84% yield. This outcome can be easily explained with the reactivity of Taxol® **1** alcohols that increase in the series 3 < < < 7 < 2'. It is worth noting that the oxazoline with the natural configuration at C-2' (R) was not detected by ^1H NMR. On the contrary, the Kingston cyclization procedure, PPh_3 in CCl_4 at 80°C, gives a mixture of C-2' oxazoline epimers.[4] The treatment of **1** with two equivalents of trifluomethanesulfonic anhydride affords the compound with a triflate on the C-7 OH, oxazoline **5**. This compound is useful for the generation

of new C-6 and C-7 derivatives.[7] The hydrolysis of the oxazoline ring is carried out using HCl 0.1N in dioxane at 50°C for 30'. If the reaction is concentrated to small volume and extracted with CH_2Cl_2 it is possible to isolate in 84% yield the hydrochloride salt **4**. Alternatively, compound **4**, in CH_2Cl_2, solution, can be smoothly and quantitatively transformed into 2'-epi-Taxol **2** by aging in CH_2Cl_2 solution at rt for 20h. After usual work up and purification by flash chromatography **2** was isolated in 86% overall yield from **3**.



Scheme 1

i: $(CF_3SO_2)_2O$ (1 eq), CH_2Cl_2, Py, -30°C → rt, 4h; ii: HCl 0.1N/dioxane 1/1, 50°C, 30'; iii CH_2Cl_2 solution, 20h; iv: $(CF_3SO_2)_2O$ (2 eq), CH_2Cl_2, Py, -30°C → rt, 5h.

Summing up, we have reported a high yield semisynthetic approach to 2'-epi-Taxol from natural Taxol (73% overall yield).

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References and Notes

1. Taxol® concentrate for intravenous infusion indications.
2. Reviews and overviews: a. Hepperle,M. And Georg,G.I. *Drugs of the Future*, **1994**, *19*, 573. b. Joel,S. *Chemistry and Industry* **1994**, 172. c. Nicolau,K.C., Dai,W.-M., Guy,R.K. **1994**, *33*, 15. d. *The Chemistry and Pharmacology of Taxol® and its Derivatives*; Farina V. Ed.; Elsevier Science: Amsterdam, 1995.
3. Unreported results from Bristol-Myers Squibb, Pharmaceutical Research Institute, Princeton, USA.
4. Kingston,D.G.I.; Chaudhary,A.G.; Gunatilaka,A.A.L.; Middleton,M.L. *Tetrahedron Lett.* **1994**, *35*, 4483.
5. All products have been fully characterized.
6. The stereochemistry of C-2' has been confirmed by n.O.e.. In fact, the n.O.e. between the C-2' and the C-3' hydrogens in the cis-oxazoline **3** is 14%, on the contrary, we observed a 8% n.O.e. when 2' hydrogen was irradiated in the trans-oxazoline with the natural configuration at C-2'.
7. New C-6,C-7 Taxol derivatives *via* C-7 alcohol triflate can be synthetized, selected examples: a. Johnson,R.A.; Nidy,E.G.; Dobrowolsky,P.J.; Gebhart,I.; Qualls,S.J.; Wicnienski,N.A.; Kelly,R.C. *Tetrahedron Lett.* **1994**, *35*, 7893. b. Chen,S.H.; Kant,J.; Mamber,S.W.; Roth,G.P.; Wei,J.M.; Vyas,D.M.; Farina,V.; Casazza,A.; Long,B.H.; Rose,W.C.; Jhonston,K.; Fairchild,C. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2223.

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