[*J. Chem. Soc., Perkin Trans. 1,* 417-421 (1998)] [Lab. of Medicinal Chemistry]

Convenient Methods for Regio- and/or Chemo-selective *O*-Deacylation of Taxinine, a Naturally Occurring Taxane Diterpenoid.

Magoichi SAKO,* Hikokazu SUZUKI, Noriyuki YAMAMOTO, Kosaku HIROTA and Yoshifumi MAKI

Regio- and/or chemo-selective *O*-deacylations of taxinine, readily available from needles of the Japanese yew *Taxus cuspidata*, at *C*-2, *C*-5, and *C*-9,10 positions have been accomplished by treatment with barium hydroxide octahydrate, sodium bis-(2-methoxyethoxy)aluminium hydride (Red-Al®), or diisobutylaluminium hydride (DIBAL-H) under mild conditions to give 2,9,10-tri-*O*-deacetyltaxinine, 2-*O*-deacetyltaxinine, 5-*O*-decinnamoyltaxinine (taxinine A), and 2,5-di-*O*-deacyltaxinine (taxuspine G), respectively, which are expected to be useful synthetic intermediates for biologically active taxinine derivatives. As interesting results, 9,10-di-*O*-deacetyltaxinine, 2-deacetyltaxinine, and taxinine A inhibited the drug-transporting function of P-glycoprotein in a high level (129-132%) compared with the case of verapamil, a typical functional inhibitor of P-glycoprotein.

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Facile Synthesis of a Novel Taxoid Closely Related to Bioactive Taxuspine D. Regio- and Stereo-selective Hydration of Taxinine, a Naturally Occurring Taxane Diterpenoid.

Hikokazu SUZUKI, Magoichi SAKO* and Kosaku HIROTA

Treatment of taxinine, which is a taxane diterpenoid readily available from needles of the Japanese yew *Taxus cuspidata*, with a large excess amount of sodium borohydride in slightly hydrous *N,N*-dimethylformamide at ambient temperature resulted in regio- and stereo-selective hydration at the C_{11},C_{12}-double bond to give an isomeric derivative of taxuspine D which exhibits remarkable inhibitory activity towards Ca^{2+}-induced depolymerization of microtubules in a manner similar to that of antitumour taxoids, Taxol® and Taxotere®, for the chemotherapeutic treatment of advanced solid cancers such as refractory ovarian cancer and metastatic breast cancer. It is notable that the hydrated product induced the differentiation of PC-12 tumour cells at concentrations of 10^{-7} mol order.

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Syntheses of Taxuspine C Derivatives as Functional Inhibitors of P-Glycoprotein, an ATP-Associated Cell-membrane Transporter.

Magoichi SAKO,* Hikokazu SUZUKI and Kosaku HIROTA

UV-Irradiation of taxinine and related compounds in acetonitrile induced a smooth transannulation between the *C*-3 and *C*-11 positions without any influence from *C*-2, *C*-9, and *C*-10 substituents to give tetracyclic taxuspine C derivatives in almost quantitative yields. Photochemical transannular reaction of taxoids possessing a cinnamoyl group in the side-chain was accompanied by an *E,Z*-isomerization of the cinnamoyl moiety. Cellular accumulation of vincristine, a useful drug for cancer chemotherapy, in multidrug-resistant ovarian cancer cells was found to increase most effectively in the case of 5-*O*-benzoylated 5-*O*-decinnamoyltaxuspine C. This indicates that the 5-*O*-benzoylated taxuspine C derivative may be a promising functional inhibitor of P-glycoprotein, which acts as an ATP-associated efflux pump for cancer chemotherapeutic agents. It should be noted that the 5-*O*-benzoylated taxoid has no remarkable cytotoxicity towards normal and cancer cells.

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Thermolysis of Taxinine and Taxinine H. Allylic Rearrangement of the Ester Moiety in the C-Ring.

Hikokazu SUZUKI, Magoichi SAKO* and Kosaku HIROTA

Thermolysis of taxinine and taxinine H, esters of 2α,9α,10β-triacetoxy-8β,12,15α,15β-tetramethyl-4-methylene-13-oxotricyclo-[9.3.1.$0^{3,8}$]pentadec-11-en-5α-ol, at the temperature of those melting points (265℃ and 230℃) in a degassed sealed tube without any solvent resulted in the smooth formation of 3-phenylacrylic acid (2α,9α,10β-triacetoxy-8β,12,15α,15β-tetramethyl-13-oxotricyclo-[9.3.1.$0^{3,8}$]pentadeca-4,11-dien-4-yl)methyl ester and acetic acid (9α,10β-diacetoxy-8β,12,15α,15β-tetramethyl-4-methylene-13-oxo-tricyclo[9.3.1.$0^{3,8}$]pentadeca-5,11-dien-2α-yl)ester by virtue of allylic migration or elimination of the 5-*O*-ester moiety, thus providing useful methods for chemical modifications of the *C*-ring in taxinine derivatives which are taxane diterpenoids readily isolable from the needles of the Japanese yew, *Taxus cuspidata*.