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

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

Regio- and/or chemo-selective O-deaclyations 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)aluminum hydride (Red-Al®), or disobutylaluminum hydride (DBAL-H) under mild conditions to give 2,9,10-tri-O-deacetylaxinine, 2-O-deacetylaxinine, 5-O-decinnamoylaxinine (taxinine A), and 2,5-di-O-deacetylaxinine (taxuspine G), respectively, which are expected to be useful synthetic intermediates for biologically active taxinine derivatives. As interesting results, 9,10-di-O-deacetylaxinine, 2-deacetylaxinine, 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.

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 Kotsaku 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 borohydrate in slightly hydrous N,N-dimethylformamide at ambient temperature resulted in regio- and stereo-selective hydration at the C₁₆, C₁₇ double bond to give an isomeric derivative of taxuspine D which exhibits remarkable inhibitory activity towards Ca²⁺-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.

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

Magoichi SAKO,* Hikokazu SUZUKI and Kotsaku HIROTA

UV-Irradiation of taxinine and related compounds in acetonitrile induced a smooth transannellation 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 cinnaomyl 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-benzyolated 5-O-decinnamoylaxuspine C. This indicates that the 5-O-benzylated 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-benzyolated taxoid has no remarkable cytotoxicity towards normal and cancer cells.

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

Hikokazu SUZUKI, Magoichi SAKO* and Kotsaku HIROTA

Thermolysis of taxinine and taxinine H, esters of 2α,9α,10β-triacetoxy-8β,12,15α,15β-tetramethyl-4-methylene-13-oxotricyclo[9.3.1.0³¹⁸]pentacont-11-en-5α-ol, at the temperature of those melting points (265°C and 230°C) in a degassed sealed tube without any solvent resulted in the smooth formation of 3-phenylalicylic acid (2α,9α,10β-triacetoxy-8β,12,15α,15β-tetramethyl-13-oxotricyclo[9.3.1.0³¹⁸]pentaconta-4,11-dien-4-yl)methyl ester and acetic acid (9α,10β-diacetoxy-8β,12,15α,15β-tetramethyl-4-methylene-13-oxotricyclo[9.3.1.0³¹⁸]pentaconta-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.