

[*Tetrahedron*, **56**, 8433-8441 (2000)]

[Lab. of Medicinal Chemistry]

**Pd/C(en)-catalyzed Chemoselective Hydrogenation with Retention of the *N*-Cbz Protective Group and Its Scope and Limitations.**

Kazuyuki HATTORI, Hironao SAJIKI and Kosaku HIROTA\*

A chemoselective method for the hydrogenation of acetylene, olefin, azide, nitro and benzyl ester functionalities with retention of the aliphatic *N*-Cbz group was established. The chemoselectivity was accomplished by using a combination of 5% Pd/C-ethylenediamine [5% Pd/C(en)] and THF (or 1,4-dioxane) as a solvent, and the scope and limitations of this methodology were investigated. Moreover, this method would increase the utility of the *N*-Cbz protective groups in organic synthesis including liquid and solid-phase peptide synthesis.

[*J. Org. Chem.*, **65**, 6670-6675 (2000)]

[Lab. of Medicinal Chemistry]

**Synthesis and Applications of [1-<sup>15</sup>N]-Labeled 4,6-Dimethyl-4*H*-[1,2,5]oxadiazolo[3,4-*d*]-pyrimidine-5,7-dione 1-Oxide as a Useful Tool for Mechanistic Investigations.**

Magoichi SAKO,\* Isamu YAEKURA, Souichi ODA and Kosaku HIROTA

[1-<sup>15</sup>N]-Labeled 4,6-dimethyl-4*H*-[1,2,5]oxadiazolo[3,4-*d*]pyrimidine-5,7-dione 1-oxide (1-<sup>15</sup>N<sub>1</sub>) was easily prepared by nitration of commercially available 6-amino-1,3-dimethyl-1*H*-pyrimidine-2,4-dione using <sup>15</sup>N-enriched nitric acid followed by an intramolecular oxidative cyclization with iodobenzene diacetate under mild conditions. On the basis of the experimental results using the labeled N-oxide 1-<sup>15</sup>N<sub>1</sub>, the formation of 8-phenyltheophylline, 1,3-dimethylalloxazines, and 1,3,7,9-tetramethyl-1*H*,9*H*-pyrimido[5,4-*g*]pteridine-2,4,6,8-tetraone in the thermal reaction of the N-oxide **1** with benzylamine, aniline, or piperidine, and the generation of nitric oxide (NO) or NO-related species in the reaction with N-acetylcysteamine were reasonably explained by considering the initial attack of the employed nucleophiles on the 3*a*-position of **1**.

[*Mol. Pharmacol.*, **58**, 1563-1569 (2000)]

[Lab. of Medicinal Chemistry]

**Reversal of P-Glycoprotein and Multidrug-Resistance Protein-Mediated Drug Resistance in KB Cells by 5-O-Benzoylated Taxinine K.**Hiroshi OKUMURA, Zhe-Sheng CHEN, Magoichi SAKO,\* Tomoyuki SUMIZAWA,  
Tatsuhiko FURUKAWA, Masaharu KOMATSU, Ryuji IKEDA, Hikokazu SUZUKI,  
Kosaku HIROTA, Takashi AIKOU and Shin-ichi AKIYAMA

5-O-Benzoylated taxinine K (BTK), a newly synthesized taxoid originally from the Japanese yew *Taxus cuspidata*, was examined for its ability to reverse P-glycoprotein (P-gp) and multidrug resistance protein (MRP)-mediated multidrug resistance. BTK reversed the resistance to paclitaxel, doxorubicin (ADM), and vincristine (VCR) of KB-8-5 and KB-C2 cells that overexpress P-gp by directly interacting with P-gp. BTK also moderately reversed the resistance to ADM of KB/MRP cells that overexpress MRP. However, BTK neither inhibited the transporting activity of MRP nor reduced intracellular glutathione levels in KB/MRP cells. BTK shifted the distribution of ADM in KB/MRP cells from punctate cytoplasmic compartments to the nucleoplasm and cytoplasm by inhibiting acidification of cytoplasmic organelles. These two functions of BTK make it able to reverse both P-gp- and MRP-mediated MDR. BTK in combination with ADM should be useful for treating patients with tumors that overexpress both P-gp and MRP.

[*J. Org. Chem.*, **65**, 258-262 (2000)]

[Lab. of Pharm. Synthetic Chemistry]

**Asymmetric Synthesis of (+)-Dihydrokawain-5-ol.**

Yoshitsugu ARAI,\* Tsutomu MASUDA, Shinya YONEDA, Yukio MASAKI and Motoo SHIRO

(+)-Dihydrokawain-5-ol was synthesized starting from the major product obtained by a highly diastereoselective Mukaiyama aldol condensation of 3-(*p*-tolylsulfanyl)furaldehyde with a silyl ketene acetal.