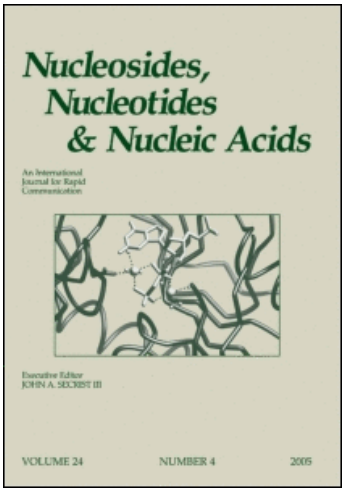

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Jun-Ichi Yamashita[a]; Hiroshi Matsumoto[a]; Kazuhiro Kobayashi[a]; Kazuharu Noguchi[a]; Mitsugi Yasumoto[a]; Tohru Ueda[b]
[a] Kodama Institute, Taiho Pharmaceutical Co., Ltd., Kodama-gun Saitama, Japan [b] Faculty of Pharmaceutical Science, Hokkaido University Kita 12, Kita-ku, Sapporo, Japan

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SYNTHESIS OF O-BENZYL DERIVATIVES OF 2'-DEOXY-5-TRIFLUOROMETHYLURIDINE FOR ANTITUMOR AGENTS

Jun-ichi Yamashita,* Hiroshi Matsumoto, Kazuhiro Kobayashi,
Kazuharu Noguchi, and Mitsugi Yasumoto

Kodama Institute, Taiho Pharmaceutical Co., Ltd.,
200-22, Toyohara, Motohara, Kamikawa-machi, Kodama-gun
Saitama 367-02, Japan

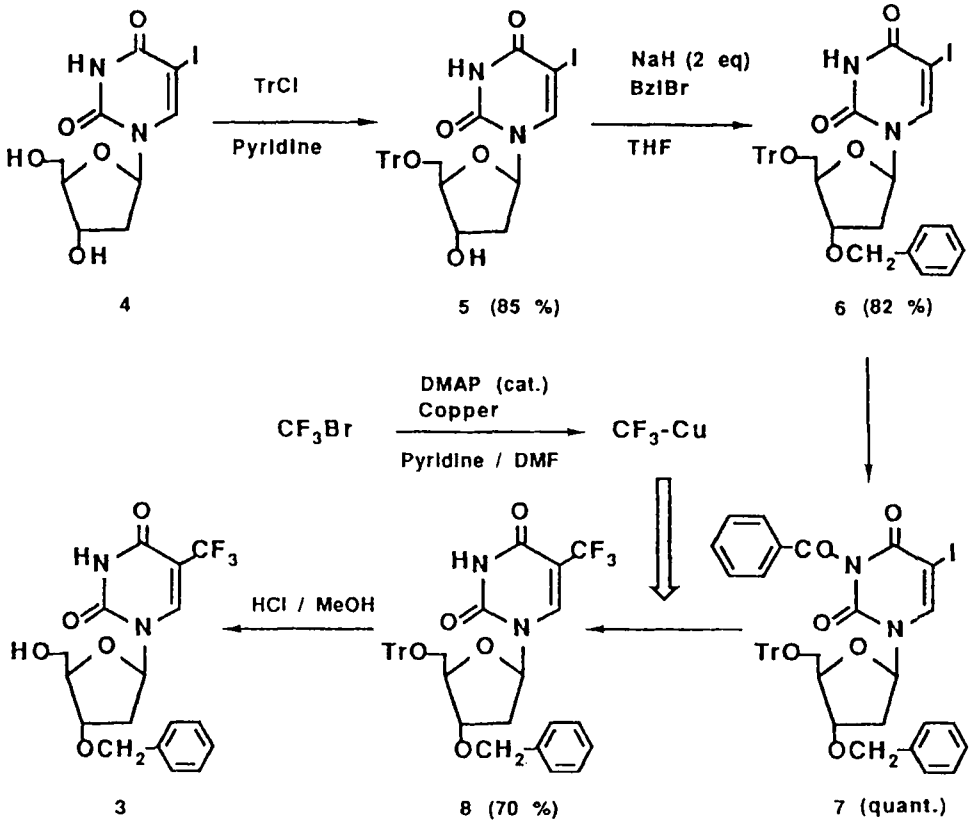
Tohru Ueda

Faculty of Pharmaceutical Science, Hokkaido University
Kita 12, Nishi 6, Kita-ku, Sapporo 060, Japan

Abstract: A practical synthesis of 3'-O-benzyl-2'-deoxy-5-trifluoromethyluridine was established which involves a selective 3'-O-benzylation of 2'-deoxy-5'-O-trityl-5-iodouridine followed by a cross-coupling with trifluoromethylcopper.

Recently, we have reported the synthesis and antitumor activities of 3'-O- and 5'-O-alkyl derivatives of 2'-deoxy-5-trifluoromethyluridine (**1**) and 2'-deoxy-5-fluorouridine (**2**).[1] Among the O-alkyl derivatives, 3'-O-benzyl-2'-deoxy-5-trifluoromethyluridine (**3**) was selected as a candidate for further clinical tests. We now selected commercially available 2'-deoxy-5-iodouridine (**4**) as a starting material and developed a cross-coupling of 3'-O-benzyl derivative of **4** with a trifluoromethylcopper complex to introduce a trifluoromethyl function. Selective O-benzylation was the first key step for the preparation of **3**. Treatment of 5'-O-trityl derivative (**5**) with benzyl bromide with two equivalents of sodium hydride in THF gave exclusively the 3'-O-benzyl derivative (**6**) in high yield.

The use of trifluoromethylcopper[2] seemed attractive if the carcinogenic solvent (HMPA) is avoided and the expensive iodotrifluoromethane is replaced with other more readily available halide. We found that heating a mixture of bromotrifluoromethane, copper powder and a



catalytic amount of 4-dimethylaminopyridine in pyridine-dimethylformamide at 115 °C gave a trifluoromethylcopper complex. Treatment of **6** (or **7**) with this complex at 60 °C gave the trifluoromethyl derivative (**8**) which was deprotected to furnish **3** in 35 % overall yield.

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2) Y. Kobayashi, K. Yamamoto, T. Asai, M. Nakano, and I. Kumadaki, J. Chem. Soc., Perkin Trans. 1, 2755 (1980).