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## Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:

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### Synthesis of O-Benzyl Derivatives of 2'-Deoxy-5-Trifluoromethyluridine for Antitumor Agents

Jun-Ichi Yamashita<sup>a</sup>; Hiroshi Matsumoto<sup>a</sup>; Kazuhiro Kobayashi<sup>a</sup>; Kazuharu Noguchi<sup>a</sup>; Mitsugi Yasumoto<sup>a</sup>; Tohru Ueda<sup>b</sup>

<sup>a</sup> Kodama Institute, Taiho Pharmaceutical Co., Ltd., Kodama-gun Saitama, Japan <sup>b</sup> Faculty of Pharmaceutical Science, Hokkaido University Kita 12, Kita-ku, Sapporo, Japan

**To cite this Article** Yamashita, Jun-Ichi , Matsumoto, Hiroshi , Kobayashi, Kazuhiro , Noguchi, Kazuharu , Yasumoto, Mitsugi and Ueda, Tohru(1989) 'Synthesis of O-Benzyl Derivatives of 2'-Deoxy-5-Trifluoromethyluridine for Antitumor Agents', *Nucleosides, Nucleotides and Nucleic Acids*, 8: 5, 1145 — 1146

**To link to this Article:** DOI: 10.1080/07328318908054313

**URL:** <http://dx.doi.org/10.1080/07328318908054313>

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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

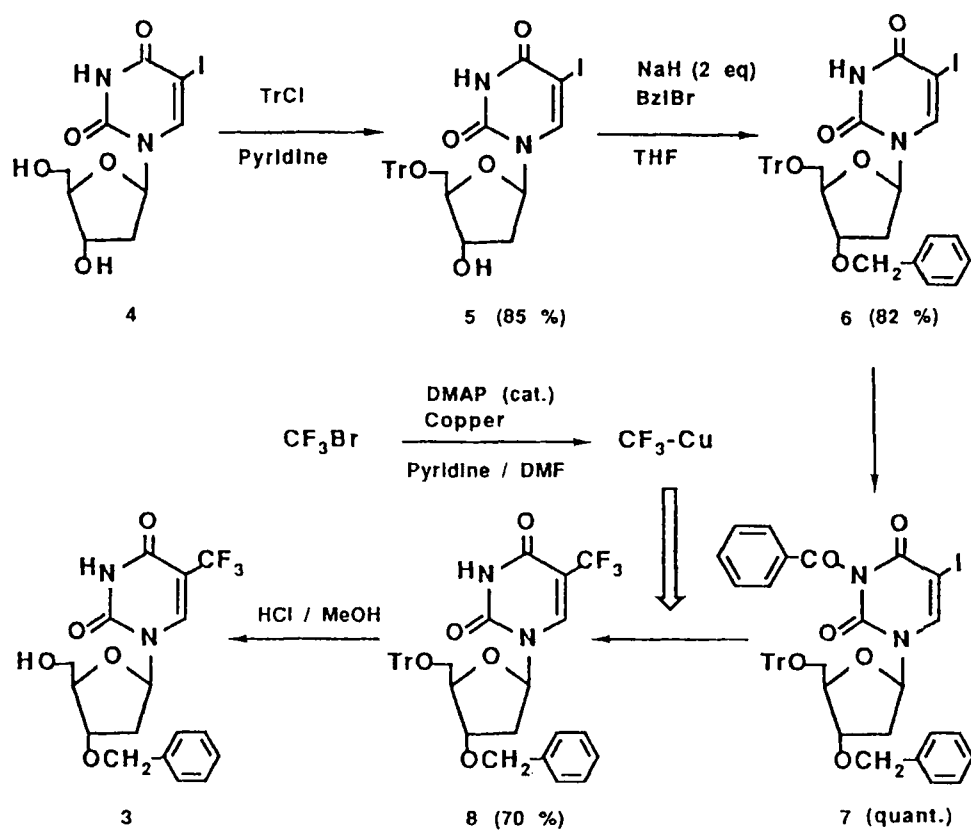
Tohru Ueda

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-benylation 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).<sup>1)</sup> 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-benylation 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<sup>2</sup> 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).