

SYNTHESIS OF 2,3,4,9-TETRAHYDROTHIOPYRANO[2,3-b]INDOLES  
VIA A NOVEL INTRAMOLECULAR INDOLE GRIGNARD REACTION

Natsuki Ishizuka and Yasuo Makisumi

Shionogi Research Laboratories, Shionogi & Co., Ltd.,  
Fukushima-ku, Osaka 553, Japan

(S)- and (R)-2 (460174-S) were synthesized in enantiomerically pure forms from oxindole and (L)-malic acid via 1 in order to obtain sufficient amounts to conduct bioassays of 2, a highly potent non-narcotic analgesic discovered in our laboratory. This synthetic method was based on our own studies of regio- and stereoselective cyclization of indole-alkylsulfides (3).

Our studies showed that metallation of 3 regiospecifically affords good yields of 4 or 5, depending on the reaction conditions, by an  $S_N2$  process under neutral and mild reaction conditions. These novel cyclization reactions were applied to 1. Mesylation of (S)- and (R)-1 in methylene chloride followed by addition of  $RMgX$  in situ at  $-20^\circ$  immediately afforded cyclization products which were converted into (S)- and (R)-2, respectively, in excellent chemical and optical yields. These novel reactions and the synthesis of 2 are described.

