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Asymmetric Synthesis of a Key Camptothecin Intermediate from 2-Fluoropyridine

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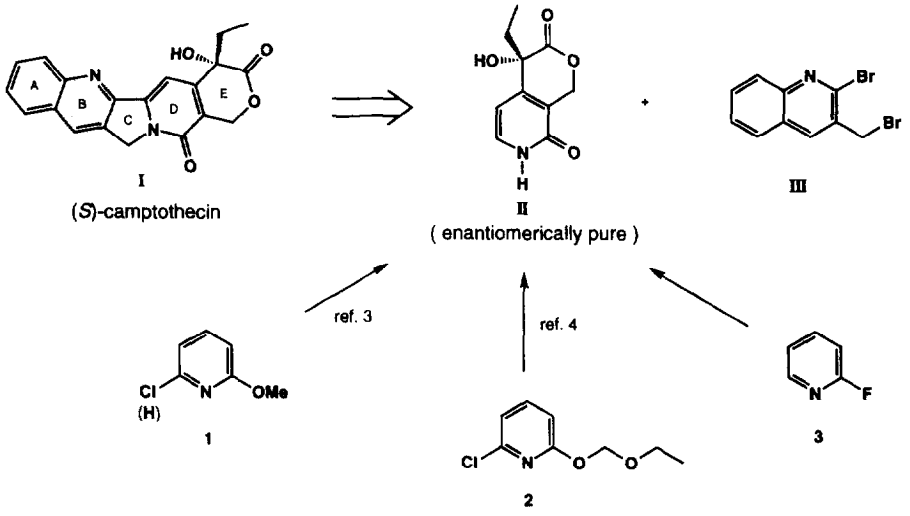
Abstract: *The DE ring camptothecin intermediate II was prepared enantioselectively in six steps from 2-fluoropyridine using a pyridine "halogen-dance" reaction.*

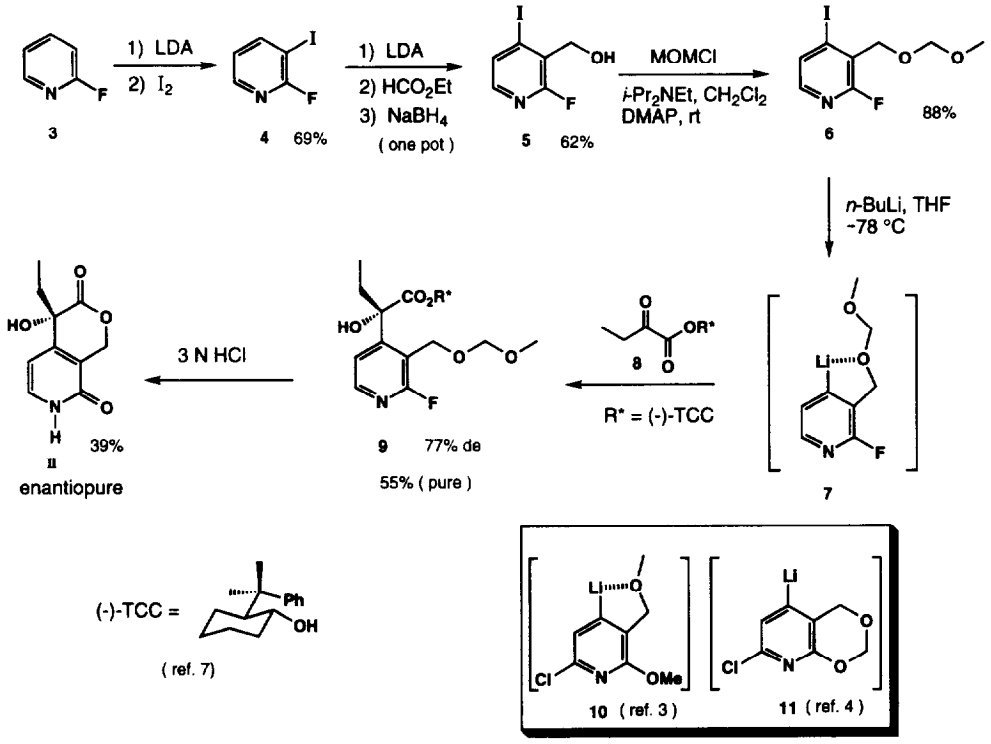
(*S*)-Camptothecin (**I**) is a naturally occurring compound found in *Camptotheca acuminata* and possesses antileukemic and antitumor properties.[1] Camptothecin has recently reemerged as one of the most important lead compounds among the anti-cancer natural products.[2] We have reported 9 and 10 step asymmetric syntheses of **I** from readily available materials.[3,4] Our synthetic approach involves coupling key intermediate **II** to bromoquinoline **III** and subsequently cyclizing the C-ring using a Heck[3] or free-radical[4] reaction. We have prepared DE ring intermediate **II** from either chloropyridine **1** or **2** in six and five steps, respectively.[3,4] As part



of a program directed at developing syntheses of camptothecin alkaloids,[5] we have been exploring new routes to the key intermediate **II**.

Reported herein is a new preparation of **II** starting from commercially available 2-fluoropyridine (**3**). The first two steps toward enantiopure **II** include an "ortho" lithiation/iodination and a pyridine "halogen-dance" reaction, both developed by Queguiner.[6] Treatment of 2-fluoropyridine **3** with LDA followed by iodine gave 2-

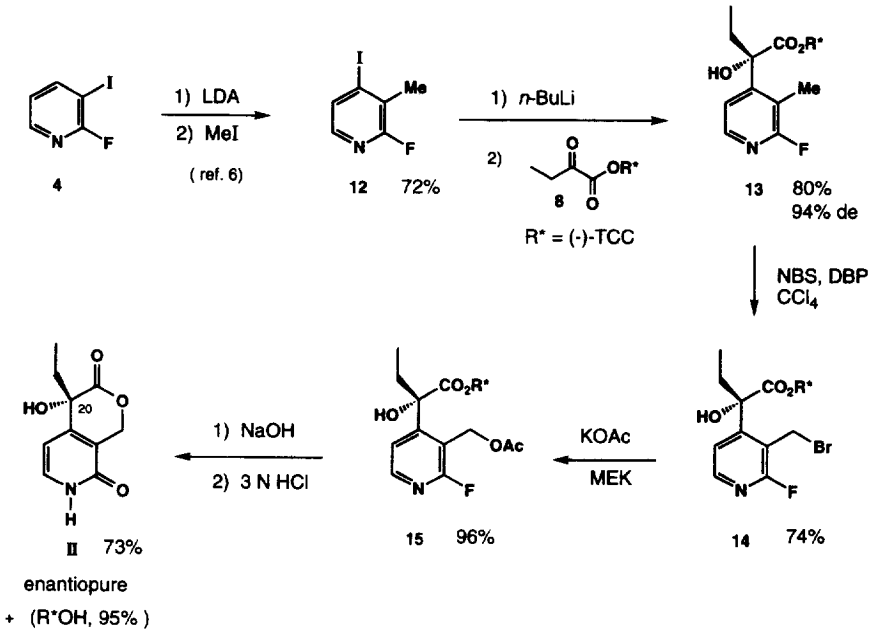
fluoro-3-iodopyridine (**4**). Addition of **4** to LDA effected the halogen-dance reaction, which was quenched with ethyl formate and worked up with $NaBH_4/H_2O$ to give alcohol **5** (mp 69-70 °C). Conversion to the MOM ether **6** and subsequent lithium-iodine exchange provided the pyridyllithium **7** in situ. Addition of chiral α-ketoester **8**,[4] prepared from α-ketobutyric acid (Aldrich) and (-)-*trans*-2-(α-cumyl)cyclohexanol ((-)-TCC),[7] provided after chromatography on silica a 55% yield of pure **9** as an oil. This reaction proceeded with a de of only 77%. Since 2-fluoropyridines are known to hydrolyze to 2-pyridones under acidic conditions,[6] we performed a one-pot conversion of **9** to **II**. Diastereomerically pure **9** was treated with 3 N HCl to give a low yield of DE ring intermediate **II**. The chiral auxiliary decomposed under these reaction conditions. Loss of the chiral auxiliary, moderate de and low overall yield prompted us to modify the synthetic route.



The lower degree of asymmetric induction observed for reaction of pyridyllithium **7** and chiral α-ketoester **8**, as compared to the analogous previous examples using pyridyllithiums **10**[3] and **11**[4] (88% de), may be attributed to increased steric hindrance or complexation due to the MOM group. To circumvent these suspected unfavorable interactions, we decided to investigate a similar synthetic sequence having only a methyl group at C-3 of a 2-fluoropyridine intermediate.

Using Queguiner's procedure,[6] treatment of **4** with LDA and quenching with methyl iodide gave trisubstituted pyridine **12** (mp 90-91 °C). Lithium-iodine exchange provided the 4-pyridyllithium in situ, which on addition of chiral α-ketoester **8** gave an 80% yield of α–hydroxyester **13** ($[\alpha]_D^{24}$ -4.1 (*c* 1.0, $CHCl_3$)) with a

de of 94% (by 500 MHz ^{1}H NMR). The C-3 methyl group was functionalized using a free-radical bromination. Treatment of **13** with *N*-bromosuccinimide and dibenzoyl peroxide in CCl_4 gave the desired bromomethylpyridine **14**.[8] Conversion of **14** to acetate **15** was carried out in 96% yield with KOAc in methyl ethyl ketone (reflux, 15 min). Hydrolysis with aqueous base, recovery of the chiral auxiliary ((-)-TCC, 95%) by ether extraction, concentration of the aqueous layer in vacuo, and treatment of the residue with 3 N HCl at reflux (21 h) gave a 73% yield of DE ring intermediate **II** [mp 228-230 °C (dec); $[\alpha]_D^{25}$ + 126.1 (*c* 0.7, MeOH)]. All properties of **II** were identical to those of material prepared by our previous routes.[3,4]



The yield of **II** from the readily available halopyridine **12**[6] is 41%. This route compares favorably to our previous two as; (1) the degree of asymmetric induction is higher, (2) the use of protecting groups is avoided, and (3) the synthetic sequence is more convenient.[9] This work compliments the recent report by Fang and coworkers[10] who prepared **II** from 2-methoxypyridine using a Sharpless catalytic asymmetric dihydroxylation to introduce the C-20 stereogenic center. We are continuing to develop other routes to camptothecin intermediate **II** and camptothecin analogs.[11]

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