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Asymmetric Synthesis of Camptothecin Alkaloids: A Nine-Step Synthesis of (*S*)-Camptothecin.

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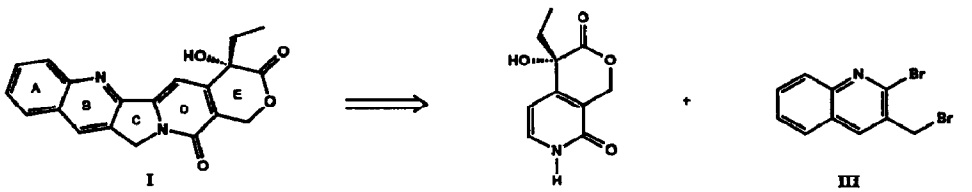
Abstract: *DE Ring camptothecin intermediate II was prepared enantioselectively from 2-chloro-6 hydroxypyridine in six steps and used in a nine-step synthesis of (S)-camptothecin.*

(*S*)-Camptothecin (**I**) continues to be one of the most important lead compounds among the anticancer natural products.[1] We recently reported a 10 step, asymmetric synthesis of **I**.[2] The synthetic sequence involved coupling key intermediate **II** to bromoquinoline **III** followed by a final C-ring cyclization using a Heck reaction.



I (*S*)-camptothecin

II (enantiomerically pure)

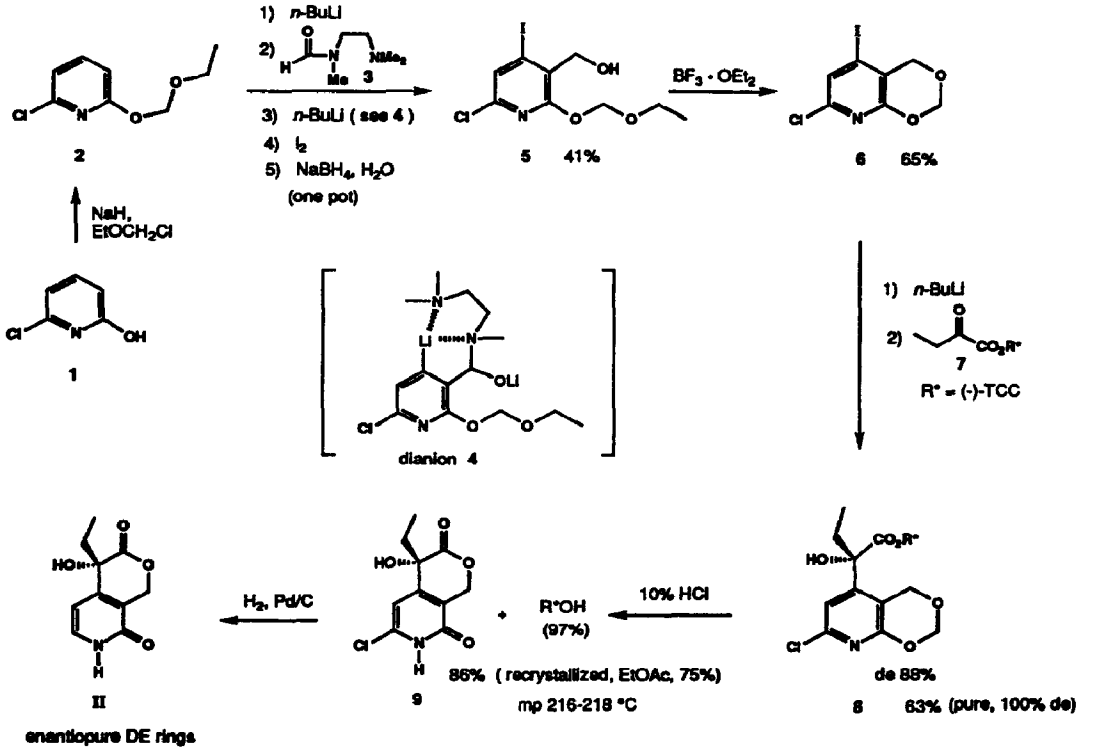
III

We are continuing to develop new routes to the DE ring intermediate **II**, and reported herein is a new preparation starting from 2-chloro-6-hydroxypyridine (**1**).

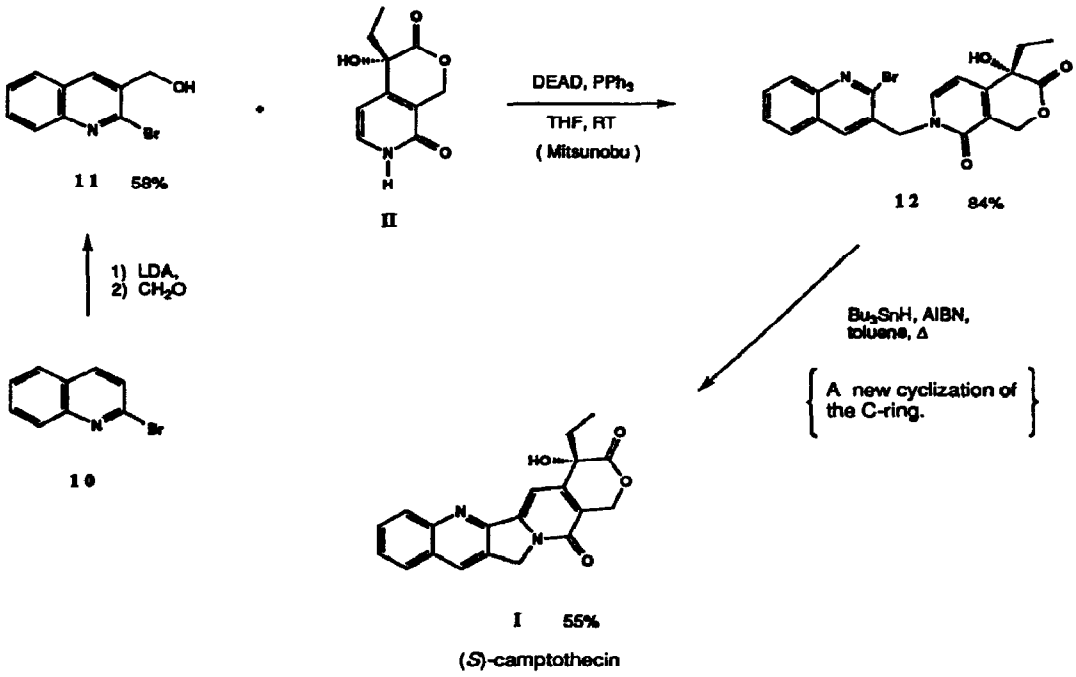
The hydroxyl group of **1** was protected on treatment with sodium hydride and chloromethyl ethyl ether in methylene chloride to give **2** (42%). The crude product contained approximately an equal amount of the *N*-alkylated product, which was easily separated by radial PLC (silica gel, 5% EtOAc/hexanes). Pyridine **2** was subjected to directed lithiation[3] (*n*-BuLi, THF, -10 °C, 10 min) and trapping with *N*-formyl-*N*,*N*',*N*'-trimethylethylenediamine[4](**3**) (-23 °C, 30 min) to give an α-amino alkoxide in situ. Addition of *n*-BuLi (-23 °C, 4 h) effected α-amino alkoxide directed lithiation[5] at C-4 to give the dianion **4**. Addition of iodine and workup with $NaBH_4$/water provided a 41% yield of alcohol **5** (mp 43-44 °C) via a one-pot process. Formation of the 1,3-dioxane **6** (mp 142-144 °C) occurred on treatment of **5** with $BF_3 \cdot OEt_2$ in methylene chloride. Lithium-iodine exchange (THF, -100 °C, 1 min) and addition of α-ketobutyrate **7**, prepared from α-ketobutyric acid (Aldrich) and (-)-*trans*-2-(α-cumyl)cyclohexanol[6] ((-)-TCC), gave the crude product **8** with a dc of 88%.

Purification by radial PLC (silica gel, 10% EtOAc/hexanes) removed the minor diastereomer and provided a 63% yield of hydroxyester **8** as an oil [$[\alpha]_D^{23}$ - 1.55° (*c* 1.1, MeOH)]. Hydrolysis of **8** with 10% HCl in methanol/water (reflux, 36 h) gave after concentration a crude solid, which was extracted twice with hot hexanes. The hexane extracts were concentrated to give recovered (-)-TCC in 97% yield. The remaining solid residue was recrystallized from EtOAc to provide a 75% yield of chloro DE rings **9** as white crystals, mp 216 - 218 °C (dec); $[\alpha]_D^{27}$ + 76.5 (*c* 1.3, MeOH) [lit.[2] mp 219 - 220 °C; $[\alpha]_D^{23}$ + 58.5 (*c* 0.85, MeOH)]. Catalytic hydrogenation of **9** gave camptothecin intermediate **II** (95%), which was identical to material prepared by our previous route.[2]

Although the overall yield of **II** is less than obtained by our previous preparation, this synthesis has some advantages: (1) *t*-BuLi is not required; (2) the chloro DE rings **9** is prepared by a simple hydrolysis of its precursor **8**; and (3) the chiral auxiliary ((-)-TCC) can be easily recovered from the crude solid product by hexane extraction.



A modification of our previous synthesis[2] was used to convert DE rings II into (*S*)-camptothecin (I). We treated 2-bromoquinoline[7] (10) with LDA and formaldehyde/THF to give alcohol 11.[8] The Mitsunobu reaction[9,10] was utilized to couple the DE rings II with 11. In this manner tetracyclic intermediate 12 was prepared in 84% yield. In our previous synthesis[2], 12 was converted to camptothecin in 59% yield using a Heck reaction.[11] For the purpose of exploring other methods for closing the C ring, we investigated a free-radical reaction. Treatment of 12 with tributyltin hydride (2 equiv) and AIBN in toluene gave a 55% yield of (*S*)-camptothecin (I), mp 272-275 °C dec; $[\alpha]_D^{23}$ + 44° (*c* 0.32, $CHCl_3$/MeOH, 4:1) [lit.[12] mp 275-278 °C dec; lit.[13] $[\alpha]_D$ + 42° (*c* 0.51, $CHCl_3$/MeOH, 4:1)]. To our knowledge this is the first example of a free-radical arylation of a 2-pyridone. Our synthetic I was identical in every respect with authentic material.[14] Work is underway to improve the overall yield of this synthesis and to develop other routes to camptothecin intermediate II and derivatives.[15]



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