# A Six-Step Synthesis of (±)-Camptothecin

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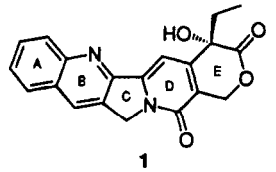
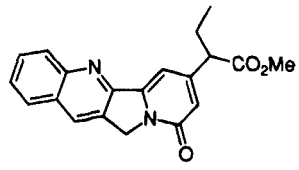
*Summary:* A six-step synthesis of (±)-camptothecin has been achieved starting from 2-methoxypyridine and 2-bromoquinoline.

The antitumor alkaloid camptothecin (**1**) has attracted much attention over the years since its isolation in 1966.[1] Camptothecin has a long, rich history[1,2] as a potential anticancer agent, and it has recently reemerged as one of the most important lead compounds among the antitumor natural products. Several syntheses of camptothecin have been accomplished, resulting in the development of numerous new synthetic strategies and methodologies.[1,3] Camptothecin proved to be a rather difficult target as is evident by the length of many of the early syntheses. Recent efforts by Danishefsky[2] and by Curran[3] were directed at finding practical and concise preparations of camptothecin alkaloids. Curran reported a six-step preparation of Danishefsky's camptothecin intermediate **2**, therefore completing an eight-step, formal total synthesis of the racemic alkaloid.[3] We recently reported a 10-step, asymmetric preparation of (*S*)-camptothecin using a chiral auxiliary-mediated synthesis.[4] Intense efforts in our laboratories have focused on improving our synthesis by reducing the number of steps required. We now report a convergent, six-step synthesis of the racemic alkaloid starting from two readily available heterocycles, 2-methoxypyridine and 2-bromoquinoline.



**1**

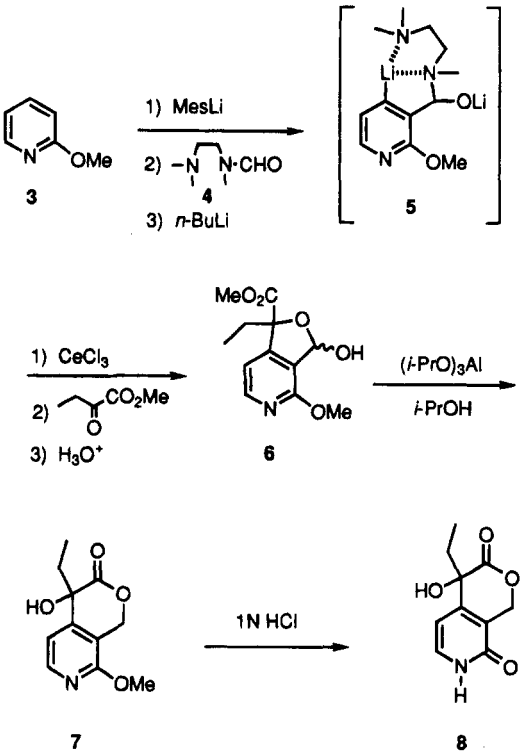
camptothecin



**2**

The strategy for shortening our camptothecin synthesis centered on finding a three-step preparation of the key DE-ring intermediate **8**. We were able to accomplish this as depicted in Scheme 1. Directed C-3 lithiation of 2-methoxypyridine (**3**) was effected using mesityllithium.[5] Treating the anion with *N*-formyl-*N*,*N*′,*N*′-trimethylethylenediamine (**4**) gave an α-amino alkoxide in situ. Addition of *n*-butyllithium (−23 °C, 2 h) effected α-amino alkoxide-directed lithiation[6] to give dianion **5**. Previous work in our laboratories had shown that dianions of the type **5** are too basic to add to enolizable α-keto esters. Attempts to reduce the basicity by metal-metal exchange using $ZnBr_2$, $MgBr_2$, and $(i\text{-PrO})_3TiCl$ were unsuccessful. Organocerium reagents prepared from organolithium or Grignard reagents are known to undergo clean addition to a wide range of enolizable carbonyl compounds.[7] When dianion **5** was added to a slurry of anhydrous $CeCl_3$ in THF at −23 °C, a homogeneous solution resulted. After being stirred for 2 h (−23 °C), the solution was cooled to −78 °C and methyl α-ketobutyrate was added in one portion. Workup and purification provided lactol **6** as a low-melting solid in 42% yield. This product is a mixture of diastereomers due to the epimerizable lactol carbon. The next step in the synthesis required conversion of the

**Scheme 1**



**3** **4** **5** **6** **7** **8**

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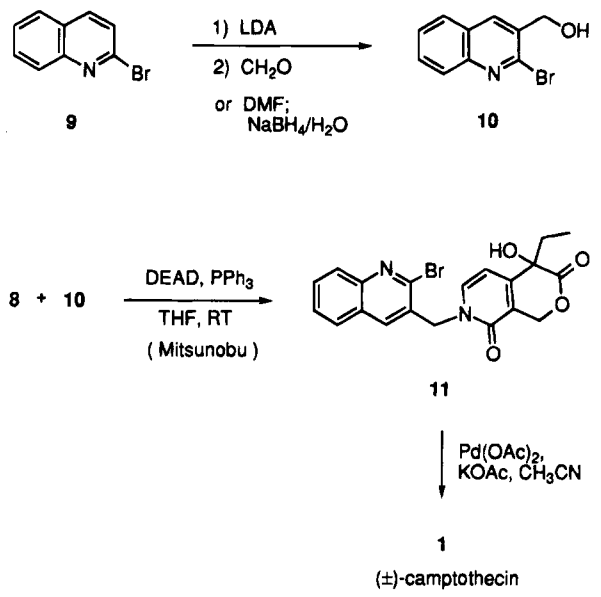
**Scheme 2**




lactol **6** to lactone **7**. Several reductions were attempted (*i.e.*, $NaCNBH_3$, $LiBH_4$, $NaBH_4$) without success. A similar problem was confronted by Stork and Schultz during the first total synthesis of (±)-camptothecin.[1d,8] The problem lies in the ease of ester reduction and the alternative reduction of the lactol to a cyclic ether. We circumvented these side reactions by resorting to the Meerwein–Ponndorf–Verley reduction.[9] Treatment of **6** with aluminum isopropoxide in 2-propanol (reflux, 3 h) gave the crude lactone **7**, which on heating with 1 N HCl (reflux, 3 h) provided the DE-ring intermediate **8** as a white solid (mp 228–229 °C, 57% from lactol **6**).

With a three-step preparation of **8** in hand, we concentrated on the AB-ring fragment. Our previous synthesis used 2-bromo-3-(bromomethyl)quinoline, prepared in two steps from 2-chloroquinoline.[4] One step would be saved if the (hydroxymethyl)quinoline **10** (Scheme 2) could be coupled directly to **8**. We prepared **10** in one step from 2-bromoquinoline via C-3 lithiation with LDA[10] and trapping with formaldehyde (58%) or more conveniently by trapping the lithiated intermediate with DMF followed with a $NaBH_4/H_2O$ workup (78%). The two fragments, **8** and **10**, were coupled using the Mitsunobu reaction[11,12] to give tetracyclic intermediate **11** in 84% yield (mp 111–112 °C). As before,[4] the C ring was closed using a Heck reaction[13] to provide a 59% yield of (±)-camptothecin (**1**), mp 275–277 °C dec (lit.[14] mp 275–277 °C). This material was identical in every respect with authentic camptothecin.[15,16]

In summary, a synthesis of (±)-camptothecin was achieved from 2-methoxypyridine and 2-bromoquinoline in six steps. The presence of an additional chiral carbon in lactol **6** complicates utilizing this approach for an asymmetric synthesis of **8**; however, efforts in this direction are underway in our laboratories.

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**Supplementary Material Available:** Experimental details for the preparation of **6**, **7**, **8**, **10**, and **11** and listings giving full spectroscopic and analytical characterization of **6**, **7**, **8**, **10**, and **11** (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(16) All new compounds were spectroscopically characterized and furnished satisfactory elemental analyses (C, H, N ± 0.4%). Details are provided in the supplementary material.