Synthesis of Functionalized Heteroaromatics: Application to Formal Total Synthesis of Camptothecin

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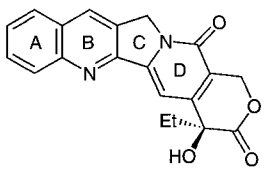
Abstract: The formal total synthesis of camptothecin was achieved *via* two types of lithiation reactions of pyridine derivatives and a Pd-catalyzed carbonylation of pyridylmethyl methanesulfonates.

Functionalization of heteroaromatics is one of important subjects in the field of pharmaceutical chemistry, since it is preferable to have heteroaromatic moieties onto drug molecules to show strong biological activities in some cases.[1] One powerful method to perform the functionalization is metallation of heretoaromatics,[2,3] and utilization of lithium derivatives is the most convenient one for this purpose.

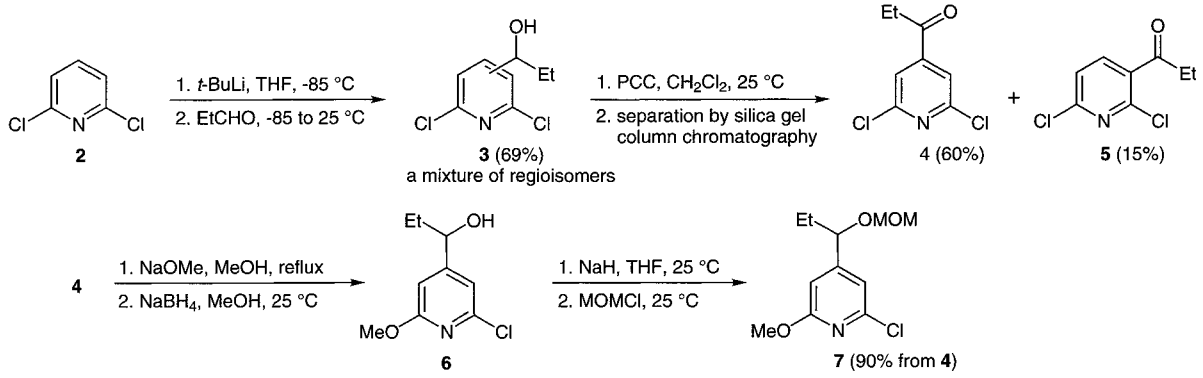
In 1966, Wall and the co-workers isolated a potent antitumor alkaloid from Chinese tree, *Camptotheca acuminata* Decene (Nyssacease), and named as camptothecin (**1**).[4] Since its inhibition mechanism of topoisomerase is different from other antitumor agents,[5] many research groups around the world have been studying camptothecin and its derivatives[6] including their synthesis.[7,8] We focused our interest on this antitumor agent and wish to report herein the synthesis of camptothecin *via* two different types of the lithiation reactions of pyridine derivatives.



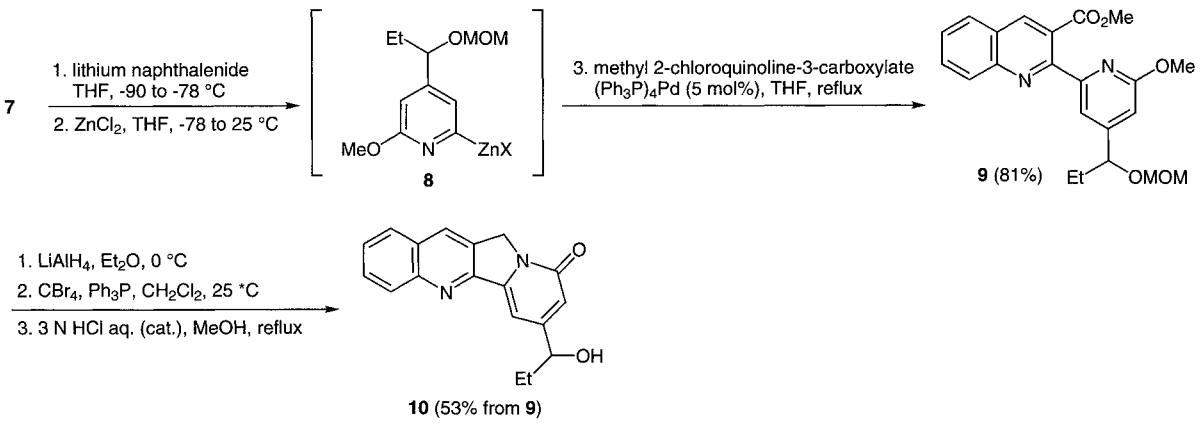
(+)-camptothecin (**1**)

Along the line of our systematic studies to synthesize functionalized hetetoaromatics,[3] we settled our synthetic strategy as starting from the construction of the D-ring of camptothecin (**1**) *via* two-different types of lithiation reactions. At first, to introduce the alkyl groups on to 2,6-dichloropyridine (**2**), we decided to perform the direct abstraction of a hydrogen on the aromatic ring by alkyllithiums.[9] To a THF solution of **2** was added 1.05 equiv. of pentane solution of *tert*-butyllithium at -85 °C followed by treatment with 1.1 equiv. of propanal to afford **3** in 69% yield as a mixture of the regioisomers. After the oxidation of **3**, the regioisomers **4** and **5** were easily separated by silica gel column chromatography. The direct lithiation did not selectively proceed, but was still convenient to perform, since this is the first step in our strategy and the regio-isomer **5** can be easily separated. To consider that the acidity of the hydrogen at the 4-position of **2** is larger than that at the 3-position, the direct lithiation of **2** could be performed selectively. There are a couple of reports that the chloride acts as the directing group during the hydrogen abstraction from the aromatic compounds by alkyllithiums.[2] The 4-lithiated compound of **2** might be isomerized into the thermodynamically more stable 3-lithiated one during the course of the reaction, although there is no experimental evidence. The ketone **4** was transformed into **7** through the following three-step conversions as shown in Scheme 1; 1) substitution of the chloride on the pyridine ring with the methoxide, 2) reduction of the ketone moiety, and 3) protection of the resulting hydroxyl group as the MOM group.

As another type of the lithiation method, the halogen-metal exchange reaction was applied to **7**. It is known that alkyllithiums sometimes directly add to the heteroaromatics when the substrate has the π-defi-



Scheme 1



Scheme 2

cient nature like pyridine, or abstract the hydrogen next to the halide group on the aromatic systems.[2] Utilization of lithium-naphthalenide complex has some advantage to achieve the halogen-metal exchange reaction without affecting other functionality on the aromatic systems. The 2-chloropyridine derivative **7** was treated with lithium-naphthalenide complex in THF at -90 °C, which was prepared *in situ* from lithium and naphthalene, to afford lithiated derivative. The resulting lithiated derivative of **7**, which was not determined, was transmetallated to the zinc derivative **8** and subjected to the Pd-catalyzed cross-coupling reaction with methyl 2-chloro-3-quinolinecarboxylate[10,11] to afford **9** in 81% overall yield. At this stage, two types of the lithiation reactions were successfully utilized in our synthesis. The coupling product **9** was further transformed into **10** *via* the reduction of the ester moiety followed by bromination, hydrolysis, and cyclization (Scheme 2).

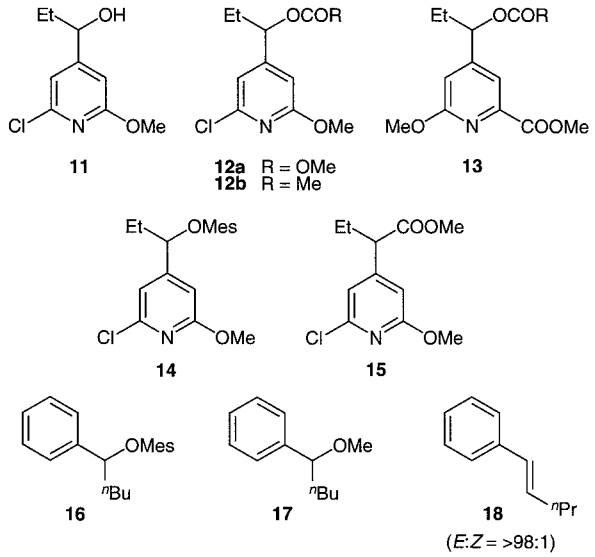
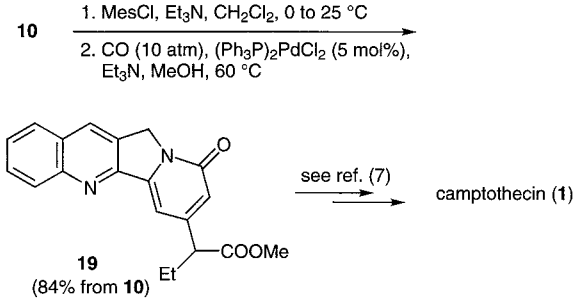


Figure 1

In order to introduce the one-carbon unit onto **10**, we decided to utilize the Pd-catalyzed carbonylation.[12] Usually, the Pd-catalyzed carbonylation at a benzylic position is performed by using benzyl halides and carbonates as the substrate.[13] So we first decided to use **11** in a model experiment to find the suitable conditions for the carbonylation. The carbonate **12a** and the acetate **12b** were prepared from **11** by the conventional methods, and were treated independently with 2 to 5 mol% of $(Ph_3P)_2PdCl_2$ and 2 equiv. of Et_3N in MeOH at 100 °C under 10 atm of CO. The recovery of **12** was obtained in ≈70% yields together with **13** (<10% yields), in which the carbonylation occurred at the 2-position on the pyridine ring instead of the pyridylmethyl position.[11] To overcome this lower reactivity, we decided to use the methanesulfonate **14** as a substrate for the reaction.[14] When **14** was subjected to the carbonylation conditions catalyzed by Pd (2.0 mol% equiv. of $(Ph_3P)_2PdCl_2$ and 2.0 equiv. of Et_3N in MeOH under 10 atm of CO at 60 °C for 10 h), **15** was only formed in 85% isolated yield. In contrast with this, when the methanesulfonate **16** was subjected to the same conditions, only **17** was produced in 96% yield. Under an atmospheric pressure of CO instead of 10 atm, **16** was converted into **18** in 86% yield selectively. It seemed that the combination of the feasibility of the leaving groups and the electron density at the benzylic position could be affected to the course of the reaction. And in the case of the π-deficient aromatics, the efficient leaving group such as methanesulfonates might be necessary to achieve the Pd-catalyzed carbonylation at the benzylic position fruitfully. Since the parent compound **10** was successfully transformed into **19** in 84% overall yield, and Danishefsky *et al.* already reported that **19** can be transformed into **1** without any problem,[6] our formal total synthesis of camptothecin *via* the functionalization of pyridine derivatives was completed at this stage (Scheme 3).



Scheme 3

Acknowledgment

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