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A FACILE SYNTHETIC METHOD OF ABCD RING SYSTEM OF ANTITUMOR ALKALOID CAMPTOTHECIN *VIA* INTRAMOLECULAR HETERO DIELS-ALDER REACTION[#]

Masahiro Toyota*, Chiyo Komori, and Masataka Ihara*

Department of Organic Chemistry, Graduate School of Pharmaceutical Sciences, Tohoku University, Aobayama, Sendai 980-8578, Japan

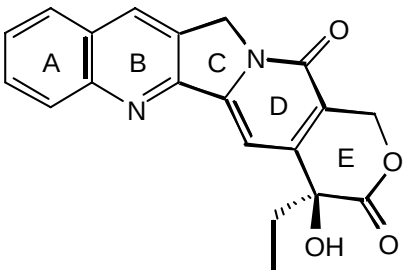
Abstract - ABCD ring system of antitumor alkaloid camptothecin (**1**), basic framework of nothapodytine B (**2**), was prepared from 2-chloro-3-hydroxy-methylquinoline (**4**) in 7 steps. The key reaction involves intramolecular hetero Diels-Alder reaction.

The discovery of the unique mechanism of the inhibition of the enzyme topoisomerase I by camptothecin **(1)** has caused a resurgence of interest in **1** and its analogs.[1] The E-ring hydroxy lactone of **1** has been **(2)** found to be a crucial structural feature with respect to its antitumor activity.[2]

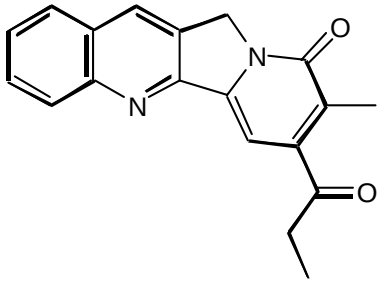
Nothapodytine B (mappicine ketone) (**2**),[3] E-ring decarboxylated analog of camptothecin (**1**), does not possess an antitumor activity, however, **2** has potent activity against the herpes viruses HSV-1, HSV-2, and human cytomegalovirus.[4] Nothapodytine B (**2**), oxidized derivative of mappicine (**3**), was initially discovered as the reaction product of **1**. Recently, **1** has been isolated from *Nothadytes foetida*,[3] however, due to low abundance of **1** in the plant, its isolation in large quantity is still difficult.

In our first contribution to this area, we would like to describe a facile synthetic method of ABCD ring system of camptothecin (**1**), basic framework of nothapodytine B (**2**), *via* intramolecular hetero Diels-Alder reaction as the key step.

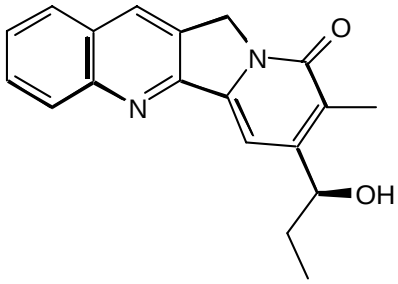
Scheme 1



Camptothecin (**1**)



Nothapodytine B (**2**)
(Mappicine ketone)



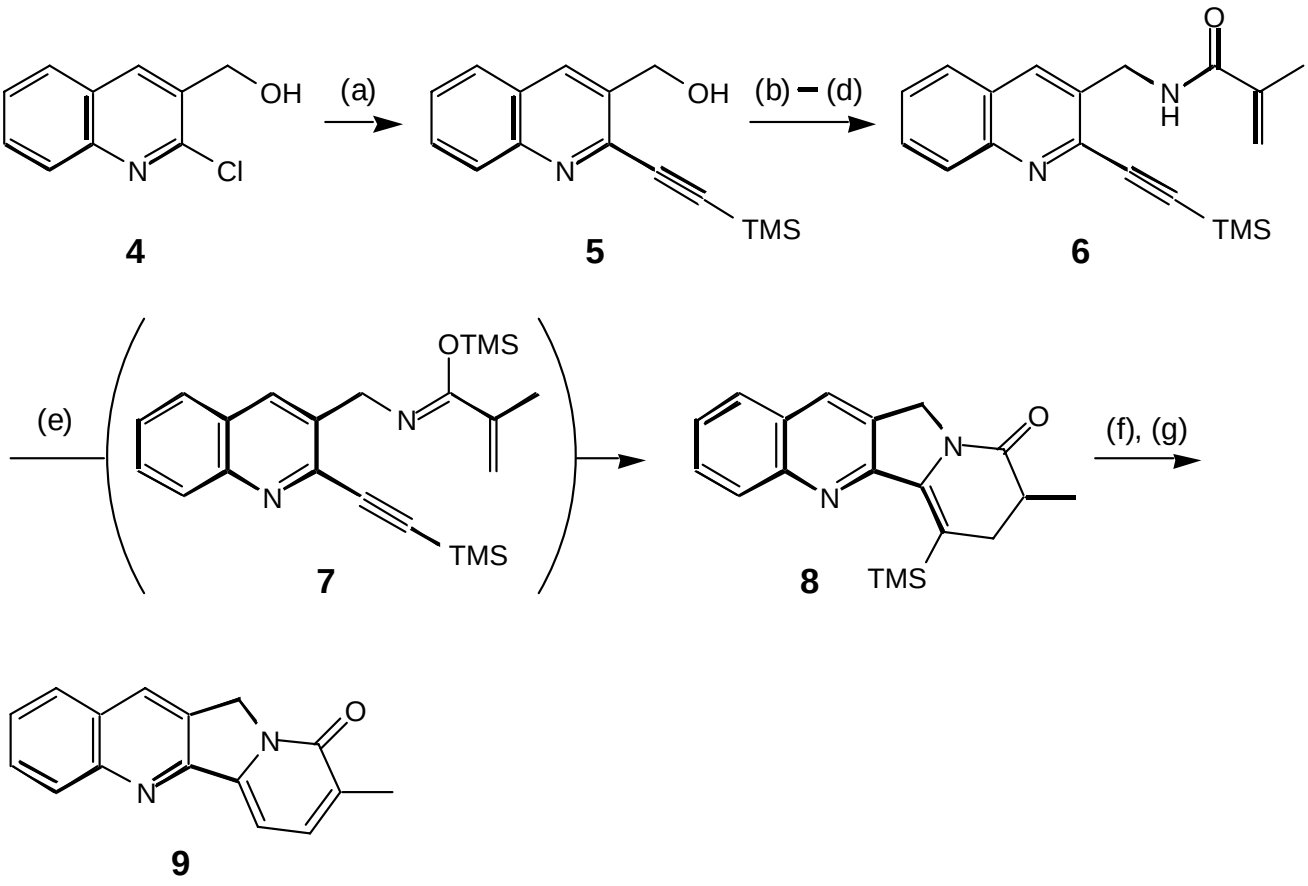
Mappicine (**3**)

The requisite substrate (**6**) for the intramolecular hetero Diels-Alder reaction was prepared as follows. Sonogashira coupling reaction[5] of the chloride (**4**) with TMS-acetylene in the presence of $Pd(PPh_3)_2Cl_2$ (5 mol %), CuI (5 mol %), and Et_3N at room temperature afforded **5** in 94% yield. After conversion of the alcohol (**5**) to the corresponding azide, reduction[6] followed by condensation of the resulting amine with methacrylic acid by means of benzotriazoyloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP)[7] furnished the amide (**6**) in 55% overall yield for 3 steps.

Intramolecular hetero Diels-Alder reaction[8] of **6** was performed in the presence of $ZnCl_2$, TMSCl and Et_3N at 180 °C in a sealed tube to lead to the tetracyclic compound (**8**) in 78% yield. Finally, desilylation (80%) followed by DDQ oxidation (78%) gave rise to the title compound (**9**).

In summary, a novel synthesis of ABCD ring system of camptothecin (**1**), basic framework of nothapodytine B (**2**), using the intramolecular hetero Diels-Alder reaction as a key step has been accomplished. Application of this novel methodology to the syntheses of **1** and **2** is in progress.

Scheme 2



Reagents and Conditions: (a) (Trimethylsilyl)acetylene, $Pd(PPh_3)_2Cl_2$ (5 mol %), CuI (5 mol %), Et_3N, DMF (94%); (b) NaN_3, CBr_4, PPh_3, DMF; (c) PPh_3, H_2O, 45 °C; (d) Methacrylic acid, BOP, Et_3N, DMF (55% for 3 steps); (e) $ZnCl_2$, TMSCl, Et_3N, toluene, 180 °C (78%); (f) 47% HBr, EtOAc (80%); (g) DDQ, C_6H_6 (78%)

REFERENCES AND NOTES

Dedicated to Professor Teruaki Mukaiyama on the occasion of his 73rd birthday.

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