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A synthesis of camptothecin

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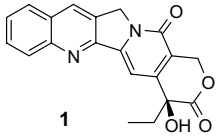
Abstract—A total synthesis of camptothecin has been carried out. Central to our synthesis is the intramolecular condensation of a suitably designed ketol, which in turn was obtained from a tricyclic ABC ring synthon. A tandem reductive amination and Michael addition sequence on an unsaturated quinoline ester was employed for the assembly of the ABC skeleton.

The isolation and characterization of camptothecin (**1**, CPT) as the active component contained in extracts from the Chinese tree, *Camptotheca acuminata*, by Wani and co-workers offered hope in 1966[1] of an antitumor therapeutic agent and triggered a great deal of interest among oncologists and synthetic chemists.[2] Activity had been demonstrated in vivo against leukemia, colon, mammary, and ovarian tumor models.[2b] Unfortunately phase 1 clinical evaluations of CPT revealed dose-limiting toxicities including myelosuppression, severe hemorrhagic cystitis, and diarrhea, which halted the clinical development.[3] Later studies pointed to the insolubility of CPT, which required the drug to be formulated as the ring-opened seco acid salt, a key aspect in its clinical failure.



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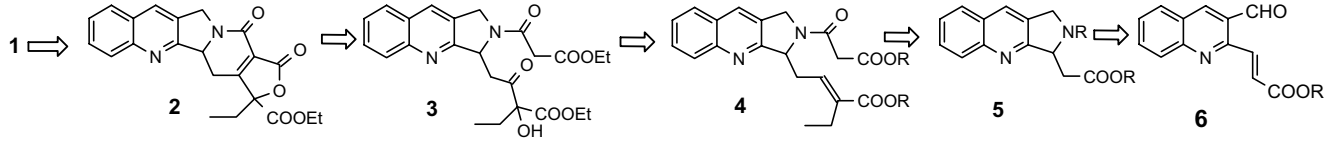
Only after topoisomerase **1** was identified by Liu and co-workers[4] as the cellular target of CPT, did its derivatives resurface as promising agents for the treatment of solid tumors by chemotherapy. A variety of total syntheses were accomplished involving novel adaptations of classical reactions as well as new chemistry inspired by the camptothecin target.[5,6] In the light of its impressive biological activity and the intriguing mode of action reported for **1**, we decided to develop a synthetic route to camptothecin amenable to the preparation of synthetic analogues.

Earlier,[6u] we exploited an intramolecular Michael addition strategy as a key step for the construction of ring D.

In this paper we describe a novel approach toward camptothecin. Central to our approach is the implementation of an intramolecular aldol reaction of ketol **3** to construct the pyridone D-ring with functionality for manipulation to the lactone E-ring of the title compounds as shown in our retrosynthetic analysis (Scheme 1). Ketol **3** was to be obtained from the tricyclic synthon **5**, the preparation of which we envisaged by a reductive amination and Michael addition using an α,β-unsaturated ester tethered aldehyde **6**.



Scheme 1.

Keywords: Camptothecin; Total synthesis; Tandem reductive amination–Michael addition; Ketol.
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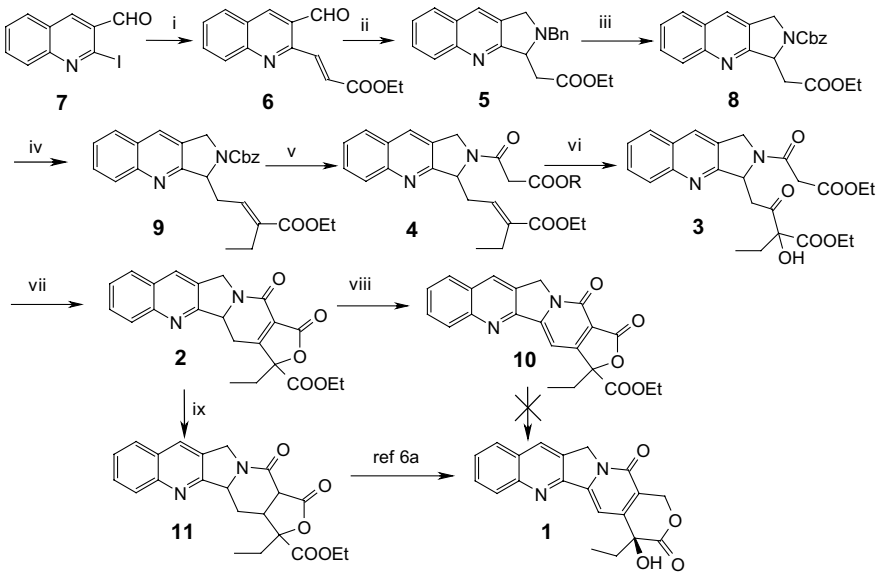

Scheme 2. Reagents and conditions: (i) ethyl acrylate, NaOAc, 5 mol % $Pd(PPh_3)_4$, DMF, 74%; (ii) (a) $BnNH_2$, MeOH, rt, 1 h, (b) $NaBH_4$, MeOH, 0 °C to rt, 2 h, 91%; (iii) (a) Pd/C–H_2, EtOH, (b) CbzCl, DCM, K_2CO_3, 90%; (iv) (a) DIBAL-H, DCM, (b) ethyl 2-(triphenylphosphoranylidene)butyrate, DCM, 80%; (v) (a) TMSCl, NaI, CH_3CN, rt, 1 h, (b) carboethoxyacetyl chloride 68%; (vi) $KMnO_4$, acetone–water, AcOH, 95%; (vii) NaH, THF, 90%; (viii) DDQ, dioxane, 90%; (ix) 10% Pd/C–H_2 (100 psi), EtOH, 88%.

The ketol **3** was prepared from Meth-Cohn's aldehyde **7** according to Scheme 2.

Thus knowing the reluctance of 2-chloro-3-formylquinoline to participate in Heck olefination[6r] we chose Meth-Cohn's 2-iodo-3-formyl quinoline **7** as the substrate, which underwent facile olefination with ethyl acrylate with $Pd(PPh_3)_4$/base/DMF to give olefin **6** in 74% yield. Condensation of **6** with benzylamine in methanol at 0 °C formed the Schiff's base that was reduced to a secondary amine at 0 °C, which subsequently underwent an intramolecular Michael addition at room temperature to form the tricyclic amine **5**. *N*-Debenzylation of **5** under hydrogenation conditions provided a secondary amine, which was protected as its benzyloxy carbamate by condensation with benzyl chloroformate. Careful reduction of this carbamate **8** with DIBAL-H resulted in the formation of an aldehyde, which was subjected to Wittig olefination with ethyl 2-(triphenylphosphoranylidene)butyrate[7] to afford the α,β-unsaturated ester **9** in good yield. Deprotection of the Cbz carbamate with TMSCl/NaI and condensation with carboethoxy acetyl chloride afforded amide **4**. $KMnO_4$ oxidation of the olefin[8] under acidic conditions furnished ketol **3**. Having obtained a substrate with the functional groups required, the stage was set to study the proposed strategy.

Pleasingly, the ketol **3** underwent an intramolecular aldol condensation with NaH in THF to furnish dihydropyridone **2**. Oxidation of the dihydropyridone with DDQ resulted in the formation of pyridone **10** which had all the functionality required for elaboration to the lactone E-ring and final adjustment of the oxidation state should have completed a synthesis of camptothecin. But to our dismay, this could not be achieved. Hence we converted the dihydropyridone **2** to the tetrahydro pyridone **11**, which has already been converted to camptothecin by Stork and Schultz.[6a] Thus careful reduction of **2** with 10% Pd–C/H_2 provided **11** and this completed a formal total synthesis of camptothecin.

In conclusion, we have developed a novel synthetic route to camptothecin **1** using an intramolecular aldol condensation reaction as a key step. This methodology could be adapted to the synthesis of analogues and enantiomerically enriched camptothecin. These studies are underway in our laboratory.

Acknowledgements

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