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Expeditious Total Syntheses of Camptothecin and 10-Hydroxycamptothecin

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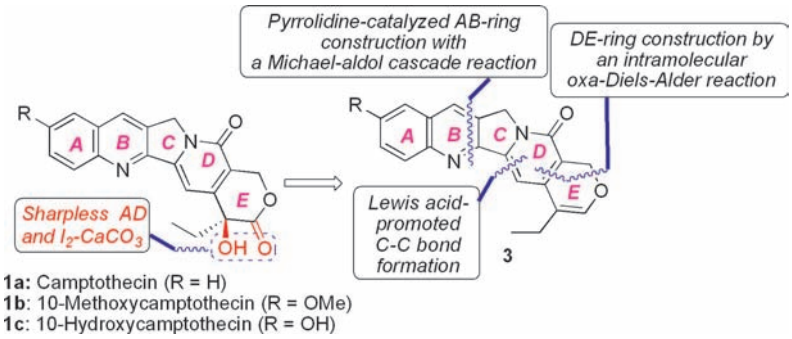
ABSTRACT



New expeditious total syntheses of (*S*)-camptothecin (16% overall yield, 95% ee) and (*S*)-10-hydroxycamptothecin (14% overall yield, 99% ee) have been accomplished, respectively, starting from readily available and inexpensive materials. Development, optimization, and successful application of the cascade reaction consisting of a pyrrolidine-catalyzed Michael addition, an intramolecular aldol condensation, and an oxidative aromatization, the intramolecular oxa Diels−Alder cycloaddition, and the Sharpless asymmetric dihydroxylation make these two new syntheses more efficient and straightforward.

Camptothecin (CPT, **1a**, Figure 1), a pentacyclic natural alkaloid isolated from *Camptotheca acuminata* (Xi Su, originated in China) by Wall and co-workers in 1966,[1] represents a unique class of complex quinoline cytotoxins which inhibit the DNA enzyme topoisomerase I (topo I). Since its isolation and structural elucidation, camptothecin has attracted considerable attention from both the academic community and the pharmaceutical industry. However, initial trials were complicated by its poor solubility and severe and unpredictable toxicity[2] until topoisomerases were discovered as the biological targets for the anticancer actions of camptothecin.[3] During the past several decades, continuous research in camptothecin-family alkaloids has led to quite a number of pharmaceutically useful camptothecin derivatives, such as topotecan (Hycamtin, **2a**, Figure 1) and irinotecan (Camptosar, **2b**).[4] Despite the rapid growth of the drug

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market, industrial sources of CPT and 10-OH CPT (**1c**) are still highly dependent on extraction from the medical plants *C. acuminata* and *Nothapodytes fetida*. As a side result, such industrial-scale extraction has brought about a shortage of natural resources and subsequent environmental problems in some developing countries. Therefore, development of efficient and economic chemical syntheses of CPT-family alkaloids, as well as the pharmaceutically useful CPT derivatives, has been an important task in organic synthesis. Many impressive total syntheses of CPT and its analogues have emerged from numerous research groups[5,6] since the first total synthesis of *rac*-camptothecin by Stock and Schultz in 1971.[7] However, involvement of difficult operations and high costs make most syntheses very impractical in the laboratory and commercial process, especially in raising materials in larger scales. Ecconomic, efficient, and easily operative syntheses of CPT and its derivatives are of much urgency and importance.

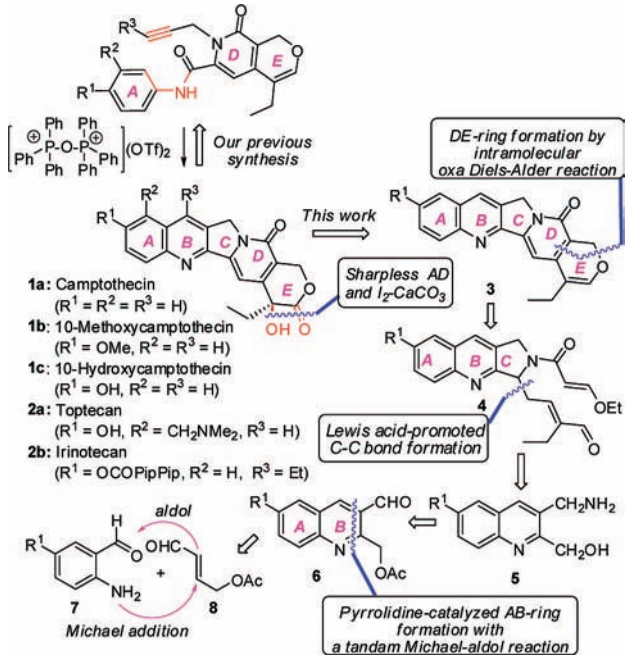

Figure 1. Camptothecin and representative derivatives, our previously used methodology, and retrosynthesis in this work.

Very recently, our laboratory disclosed a short and efficient route which is generally applicable to this class of alkaloids and their analogues.[8] In that synthesis, a mild oxodiphosphonium-promoted cascade reaction consisting of an imidate formation, an intramolecular aza-Diels−Alder reaction and an eliminative aromatization was optimized and successfully employed to construct the common key tetracyclic A/B/C/D-ring core of CPT-family alkaloids in high yield (Figure 1). However, multiple air-sensitive organometallic reagents were used in the preparation of the key pyridone precursor (the D/E ring of CPT).[9] This is disadvantageous especially for large-scale synthesis in the future. In order to achieve a more practical and efficient total synthesis, we herein present a new expeditious and straightforward route for this family of biologically important alkaloids. In this synthesis, a secondary amine-catalyzed cascade reaction was employed to the preparation of the A/B ring and an inverse electron demand intramolecular oxa Diels−Alder reaction served as the protocol for constructing the D/E ring.

In view of the efficiency in constructing a multiring system, we envisioned that formation of the D/E ring of CPT (**1a**) and 10-hydroxycamptothecin (10-OH CPT, **1c**) could be commonly accomplished by an inverse electron demand intramolecular oxa Diels−Alder reaction in a later stage of the total synthesis. Such a one-step protocol is novel and quite different from the literature works in constructing the D/E ring. More advantageously, such a treatment will avoid the use of sensitive and expensive organometallic reagents. In the meantime, synthesis of the A/B ring in this study was designed to utilize an economic cascade reaction combination, which consists of a pyrrolidine-catalyzed Michael addition and an intramolecular aldol condensation and an oxidative aromatization as the end. According to this retroanalysis, two simple, inexpensive, and readily available materials, *o*-aminobenzaldehyde **7** and α,*β*-unsaturated aldehyde **8**, would serve as the starting materials in this new total synthesis.

Development and utilization of novel cascade reactions are a particularly attractive strategy in the synthesis of complex molecular architectures to achieve the highly efficient formation of multiple C−C bonds in one operation.[10] In this study, we started our new total syntheses of CPT and 10-OH CPT from the optimization of an efficient Michael addition−aldol condensation cascade,[11] serving as a powerful method for construction of the A/B ring of CPT alkaloids (Scheme 1). In the presence of catalytic amounts of pyrrolidine (10 mol %) and benzoic acid (10 mol %), reactions of α,*β*-unsaturated aldehyde **8** with 2-aminobenzaldehydes **7** could be performed smoothly in dichloromethane at room temperature, affording two inseparable

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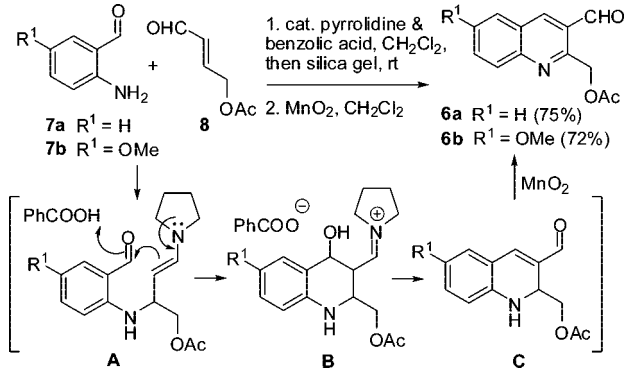
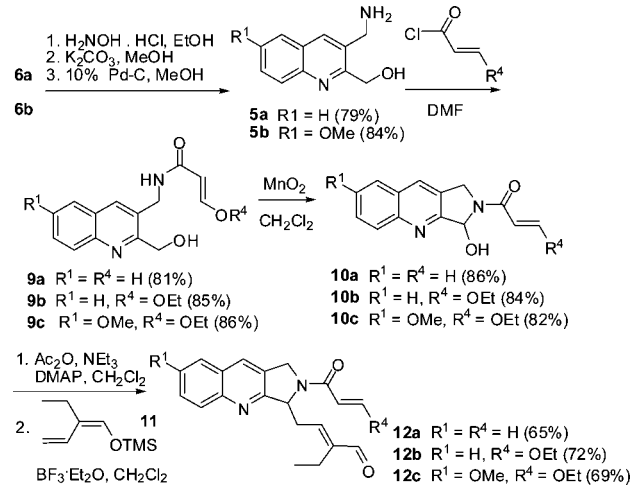
products. The minor one in the resulting mixture was finally identified, by careful ^{1}H NMR analysis, as an imine byproduct. This imine was formed by the reaction between the desired product (benzaldehyde **C**) and the excess of aniline reactant **7**. Fortunately, the above-mentioned byproduct could be fully convert to the required aldehyde **C** by a simple treatment with silica gel at room temperature. After removal of silica gel by filtration, the resulting solution was directly treated with the freshly prepared MnO_2 to afford quinolines **6** in satisfactory overall yields (75% for **6a** and 72% for **6b**). Using the above mild pyrroline-catalyzed cascade reaction and subsequent treatment with MnO_2, elaboration of the A/B ring system was efficient accomplished in a short fashion. The workups involved in the above transformations were very convenient and practical in laboratory, and only one chromatographic purification was required.

Scheme 1. Construction of Quinoline Precursors **6** by Pyrrolidine-Catalyzed Michael Addition−Aldol Condensation Cascade Reaction



Sequential three-step treatment (without purification of intermediates) was adopted to convert the quinolinyl adhedydes **6** into the corresponding amine precursors **5** (Scheme 2). Oximation of the benzaldehydes **6** with NH_2OH, removal of the acetate with K_2CO_3 in methanol and followed by hydrogenation (1 atm) of oxime in methanol with 10% Pd−C at room temperature provided the corresponding benzylamines **5** in satisfactory yields (79% for **5a** and 84% for **5b**). Parallel acylation of amines **5** with acryloyl chloride or 3-ethoxyacryloyl chloride in DMF yielded the corresponding acrylamides **9** (81% for **9a**, 85% for **9b**, and 86% for **9c**), respectively. MnO_2-based oxidation of quinolin-2-ylmethanols **9** was mildly carried out in dichloromethane, giving the aminal derivatives **10** (86% for **10a**, 84% for **10b**, and 82% for **10c**). Acetylation of aminals **10** followed by treatment with enol silyl ether **11**[12] in the presence of BF_3•Et_2O at −78 °C[13] furnished the substrates **12** in satisfactory yields (65% for **12a**, 72% for **12b**, and 69% for **12c**) for the following oxa Diels−Alder reactions.

Scheme 2. Syntheses of ABC-Ring Intermediates **12**



The crucial inverse-electron-demand intramolecular oxa-Diels−Alder reactions were examined in mesitylene at 160 °C in a sealed tube (Table 1).[14] Significant electronic effects of the dienophiles were observed. Using simpler **12a** (R^4 = H) as the substrate, all attempts failed including optimizations in reaction temperatures, solvents, Lewis acids, ultrasound, neat conditions, etc. Instead, decompositions were frequently found. Common knowledge in this type of reactions mentioned that the substrate modification by tuning the electronic property of the dienophile would be favorable. Thus, an electron-donating ethoxyl group was introduced at the β-position of unsaturated amide substrate **12** to strengthen the interactions between the LUMO of the diene and the HOMO of the dienophile. To our delight, thermal cycloaddition of the modified substrate **12b** (R^4 = OEt) proceeded smoothly, providing two separable diastereomers (**13ba** and **13bb**, 3:1) in an excellent total yield (83%). This reaction was surprisingly clean and none other theoretically possible diastereomeric cycloadducts and byproducts were detected. The relative configurations of these two products were determined by NOESY experiments, as well as the X-ray single crystallography of **13ba** (see Supporting Information). Similarly, substrate **12c** also gave two diastereomers **13ca** and **13cb** (9:1) in 92% total yield. Both diastereomeric

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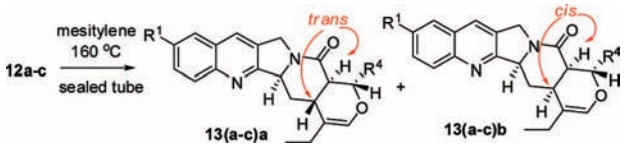
products *trans*-**13(b−c)a** and *cis*-**13(b−c)b** are eligible for our following synthesis.

Table 1. Intramolecular Oxa Diels−Alder Reactions[a]

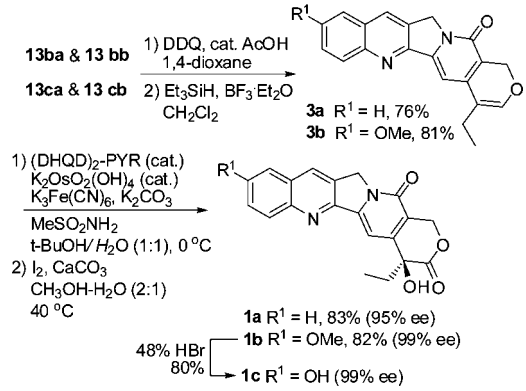


entry	reactant	products[b]	yield[c] (%)
1	**12a**: $R^1 = R^4 = H$	complicated	
2	**12b**: $R^1 = H$, $R^4 = OEt$	**13ba**:**13bb** = 3:1	83
3	**12c:** $R^1 = OMe$, $R^4 = OEt$	**13ca**:**13cb** = 9:1	92

[a] The reactions were performed in mesitylene in a sealed tube at 160 °C. [b] **13ba** was confirmed by single-crystal X-ray crystallography. [c] Total isolated yield of both diastereomers.

With the pentacyclic precursors **13** in hand, our endeavor continued toward the total syntheses of CPT and 10-OH CPT. Treatment of the mixture of **13ba** and **13bb** with DDQ and a catalytic amount of CH_3COOH in 1,4-dioxane[15] followed by reductive removal of the ethoxy group[16] afforded CPT precursor **3a** in 76% yield (Scheme 3). Accordingly, the other

Scheme 3. Completion of Total Syntheses of Camptothecin and 10-Hydroxyoxycamptothecin



mixture of **13ca** and **13cb** provided **3b** in 81% yield. Further oxidative transformations (Sharpless asymmemetric dihydroxylation followed by $I_2/CaCO_3$-based hemiacetal oxidation)[8a] successfully converted the cylic enol−ethers **3a** and **3b** to camptothecin (**1a**) and 10-methoxycamptothecin (**1b**), respectively. In addition to CPT (83% yield, 95% ee),[8a] 10-methoxycamptothecin (**1b**) was afforded in 82% yield and 99% ee (by HPLC, see Supporting Information). Final demethylation of **1b** with 48% aqueous HBr[17] in a sealed tube provided 10-hydroxycamptothecin (**1c**, 80%, 99% ee by HPLC), the common industrial material in prodcutions of anticancer drugs topotecan (**2a**) and irinotecan (**2b**). All aspects of the synthesized camptothecin (**1a**) and 10-hydroxycamptothecin (**1c**) are in well agreement with those of natural products.

In summary, new expeditious total syntheses of (*S*)-camptothecin (16% overall yield, 95% ee) and (*S*)-10-hydroxycamptothecin (14% overall yield, 99% ee) have been accomplished, respectively, starting from simple, readily available, and inexpensive materials. Development, optimization, and successful application of the cascade reaction consisting of a pyrrolidine-catalyzed Michael addition, an intramolecular aldol condensation, and an oxidative aromatization, the intramoculecular oxa Diels−Alder cycloaddition, and the Sharpless asymmetric dihydroxylation make these two new syntheses more efficient and straightforward. Mild conditions, minimal use of the chromatographic purifications, and avoiding the use of sensitive organometallic reagents in many transformations are advantageous and convenient for construction of the multiple ring system of CPT-family alkaloids. The achieved syntheses and newly developed methodologies will be valuable in future endeavors for an economic industrial process of CPT alkaloids and their derivatives.

Acknowledgment. This work is financially supported by NSFC (20425205, 20621062) and CAS (KJCX2-YW-H08).

Supporting Information Available: Experimental details and full characterization of new compounds, copies of NMR spectra of new compounds, HPLC analyses of synthetic (*S*)-**1b** and (*S*)-**1c**), and X-ray crystal data of **13ba**.This material is available free of charge via the Internet at http://pubs.acs.org.

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