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Highly Efficient and Mild Cascade Reactions Triggered by Bis(triphenyl)oxodiphosphonium Trifluoromethanesulfonate and a Concise Total Synthesis of Camptothecin

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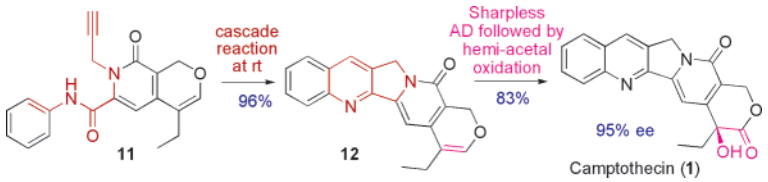
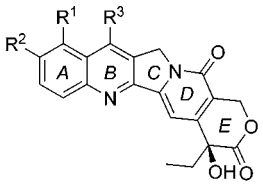
ABSTRACT



A mild and efficient cascade methodology is reported to construct variously substituted indolizino[1,2-*b*]quinolin-9(11*H*)-ones. Efficiently triggered by bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate under mild conditions, this cascade achieved significant enhancements in chemical yields. Utilizing this highly efficient domino reaction followed by a Sharpless dihydroxylation, an eight-step total synthesis of camptothecin was accomplished from a known pyridine derivative in direct fashion with an overall yield of 47% and 95% ee.

The potent antitumor activities and clinical applications of the camptothecin family of alkaloids have attracted intense interest worldwide. Camptothecin (CPT, **1**, Figure 1) was isolated from the Chinese plant *Camptotheca acuminata* in 1966 by Wani and Wall.[1] The primary cellular target of CPT is the covalent binary complex formed between DNA and topoisomerase I during DNA relaxation, and the stabilization of this complex by CPT is believed to lead to cell death.[2] Many imaginative syntheses of camptothecin and its analogues have emerged from numerous research groups over



Camptothecin (**1**: R^1=R^2=R^3=H)
Toptecan (**2a**: R^1=CH_2NMe_2, R^2=OH, R^3=H)
Irinotecan (**2b**: R^1=H, R^2=OCOPipPip, R^3=Et)

Figure 1. Camptothecin and two representative derivatives.

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the past decades.[3] The summit of these efforts occurred when two camptothecin analogues, topotecan (**2a**)[4] and irinotecan (**2b**),[5] were approved by the FDA to treat cancers. Additionally, several analogues reached different stages of clinical trials.[6] Thus, development of practical and efficient strategies for acquiring new CPT derivatives is of great value. However, to date, the chemical synthesis of camptothecin remains a challenge since most of the known syntheses are lengthy, of low overall efficiency, and of high cost as compared with natural sources.

By retrosynthetic analysis of CPT, concomitant construction of the indolizino[1,2-*b*]quinolin-9(11*H*)-one B and C rings by using an intramolecular aza-Diels−Alder reaction[3a] could theoretically achieve the highest efficiency (Figure 2).

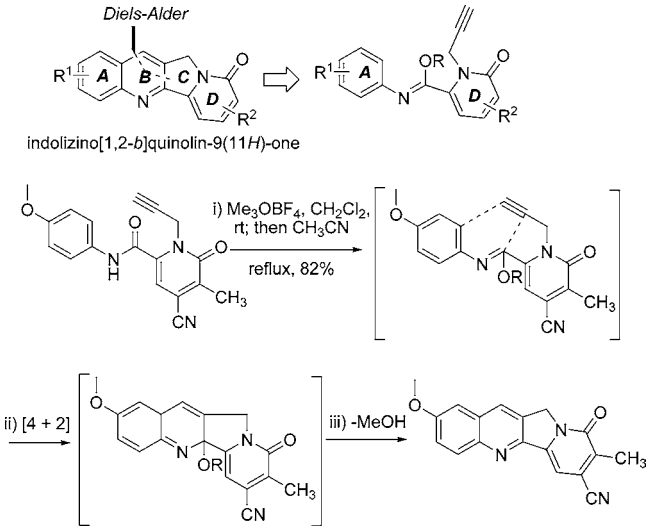


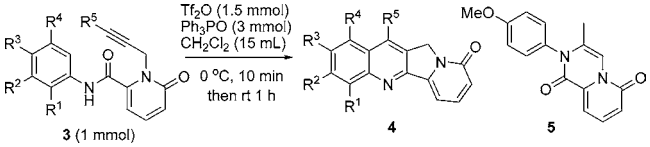
Figure 2. Intramolecular aza-Diels−Alder reaction-based retrosynthesis of the indolizino[1,2-*b*]quinolin-9(11*H*)-one core of CPT, and a previous approach by Fortunak et al. using a cascade reaction.

A previous synthesis by Fortunak and co-workers validated the practicality of this approach.[7] However, Fortunak's method has limitations related to chemical yields, byproducts, and the scope of the reaction. In this intramolecular hetero-Diels−Alder reaction, an alkyne serves as the dienophile and an *N*-arylimidate serves as the diene (presenting a double-bond equivalence in aryl ring A, which serves as one 2π component together with an in situ formed imidate C═N bond). Consideration of reaction mechanisms indicates that a critical step to initiate the domino reaction sequence is the in situ formation of imidates through activation of corresponding chemically stable amides.

To optimize this reaction, we screened a variety of amide-activating reagents using as substrate amide **3a** (see Table 1). With trimethyloxonium fluoroborate (previously used by Fortunak et al.[7]), the expected product **4a** was isolated in only 12% yield, with the concomitant formation of byproduct **5** in 5% yield. The highest yield achieved after optimizations was only 32% when using dichloromethane as solvent under reflux. We were not able to achieve the reported yield of 65% for **4a**.[7] Attempts with other Lewis acids also failed to give satisfactory results.

Bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate (prepared by in situ combination of 1 equiv of Tf_2O and 2 equiv of Ph_3PO in dichloromethane at 0 °C) has been recently used for the synthesis of thiazolines and imidazoline-containing amino acids by Kelly and co-workers.[8] According to the proposed mechanisms, such a reagent should serve as

Table 1. Synthesis of Indolizino[1,2-*b*]quinolin-9(11*H*)-ones with Bis(triphenyl)oxodiphosphonium Trifluoromethanesulfonate[12]



entry	reactant	product(s)	yield (%)
1	**3a**: $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = OMe$	**4a**: $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = OMe$	90
2	**3b**: all R = H	**4b**: all R = H	98
3	**3c**: $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = NMe_2$	**4c**: $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = NMe_2$	95[a]
4	**3d**: $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = Me$	**4d**: $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = Me$	98
5	**3e**: $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = Br$	**4e**: $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = Br$	95
6	**3f**: $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = F$	**4f**: $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = F$	95
7	**3g**: $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = CO_2Me$	**4g**: $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = CO_2Me$	91
8	**3h**, $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = CN$	**4h**, $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = CN$	99[b]
9	**3i**: $R^1 = R^3 = R^4 = R^5 = H$, $R^2 = Me$	**4i**: $R^1 = R^3 = R^4 = R^5 = H$, $R^2 = Me$ **4i′**: $R^1 = R^2 = R^3 = R^5 = H$, $R^4 = Me$	98 **4i**:**4i′** = 3:2
10	**3j**: $R^2 = R^3 = R^4 = R^5 = H$, $R^1 = Me$	**4j**: $R^2 = R^3 = R^4 = R^5 = H$, $R^1 = Me$	94
11	**3k**: $R^1 = R^3 = R^5 = H$, $R^2 = R^4 = Me$	**4k**: $R^1 = R^3 = R^5 = H$, $R^2 = R^4 = Me$	98
12	**3*l***: $R^1 = R^2 = R^3 = R^4 = H$, $R^5 = Et$	**4*l***: $R^1 = R^2 = R^3 = R^4 = H$, $R^5 = Et$	100

[a] The yield is based on 55% recovery of **3c**. [b] The yield is based on 63% recovery of **3h**.

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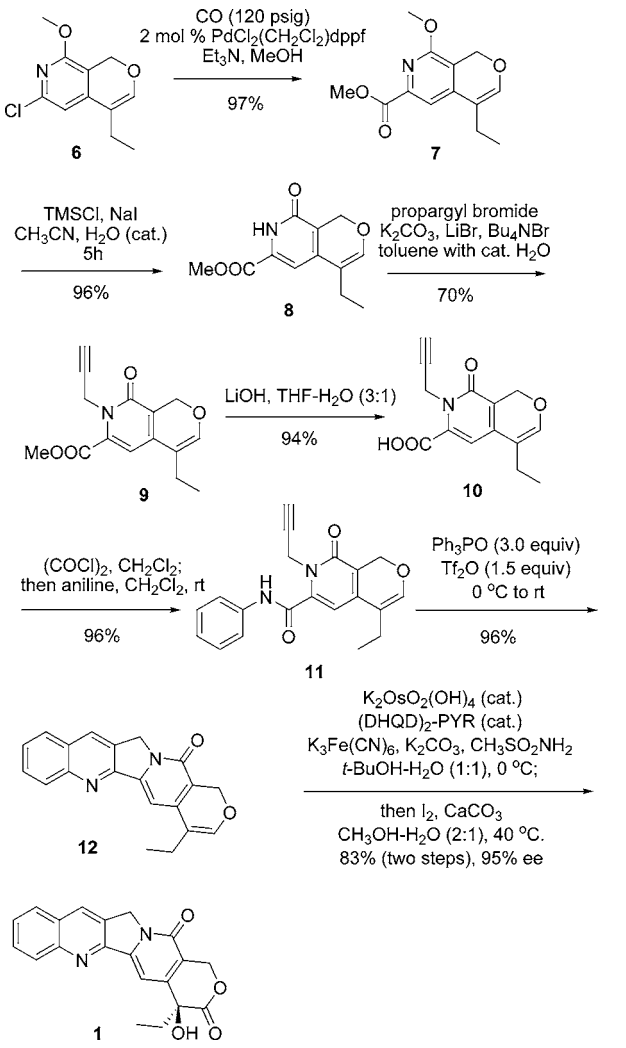
an activator to convert an amide to its corresponding imidate under mild conditions, and to promote the subsequent intramolecular aza-Diels−Alder annulation in the desired direction. To our delight, treatment of amide **3a** with bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate at room temperature afforded the desired tetracyclic product **4a** in excellent isolated yield (Table 1, entry 1). After optimization, the best reaction conditions were achieved with 3 equiv of Ph_3PO and 1.5 equiv of Tf_2O in CH_2Cl_2 from 0 °C to room temperature. Encouraged by the initial results, we examined the generality of this reaction. All substrates (**3b**−***l***) were subjected to the optimized conditions and the reactions proceeded smoothly at ambient temperature, giving the corresponding indolizino[1,2-*b*]quinolin-9(11*H*)-ones (**4b**−***l***) in nearly quantitative yields (Table 1). All the substrates except **3i** afforded single products. In the case of **3i**, a mixture of regioisomers **4i** and **4i′** (**4i**:**4i′** = 3:2, measured by ^{1}H NMR) was afforded. Thus, the use of Tf_2O−$2Ph_3PO$ as an amide activator provides a mild, facile, and general approach to synthesize variously substituted indolizino[1,2-*b*]quinolin-9(11*H*)-ones through a highly efficient cascade sequence involving intramolecular aza-Diels−Alder reaction at ambient temperature.

Total synthesis of camptothecin (**1**) with this mild and efficient cascade reaction started from the known chloropyridine **6**[9] (Scheme 1). Carbonylation of **6** was accomplished smoothly in methanol under CO atmosphere (120 psig) at 90 °C in the presence of 2 mol % of $PdCl_2(CH_2Cl_2)$dppf and Et_3N, affording the methyl ester **7** (97%). Selective *O*-demethylation of **7** with iodotrimethylsilane (generated in situ from TMSCl and sodium iodide) in acetonitrile afforded pyridone **8** (96%).[10] *N*-Propargylation of **8** was carried out with propargyl bromide, K_2CO_3, tetrabutylammonium bromide, and LiBr in toluene, giving the new pyridone **9** (70%). Basic hydrolysis of methyl ester **9** gave the corresponding carboxylic acid **10** (94%). Treatment of **10** with oxalyl chloride followed by coupling with aniline afforded the stable amide precursor **11** (96%). Employing the newly developed cascade annulation methodology, an advanced intermediate **12**[11] containing the whole skeleton of CPT was obtained in 96% yield by simple treatment of amide **11** with bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate at room temperature.

Transformation of **12** to camptothecin (**1**) was recently carried out by a two-step procedure[11] involving a Sharpless asymmetric dihydroxylation and an $I_2/CaCO_3$-based hemiacetal oxidation in a relatively low yield (33%). Satisfactory results were finally achieved after our modification of these two reactions. Optimizing the mixed solvent from 10:1 (MeOH−H_2O) to 2:1 (MeOH−H_2O) greatly improved the reaction efficiency and yield in the hemiacetal oxidation. By using this modified procedure, camptothecin (**1**) was synthesized in 83% yield (2 steps) and 95% ee (measured by a chiral HPLC, 99% ee after a simple recrystallization (71%) from 1,4-dioxane, $[\alpha]^{20}_D$ 41.6 (*c* 0.2, $CHCl_3$−MeOH 4:1)).[10] Thus, a short total synthesis of (+)-camptothecin was accomplished in 8 steps from the known pyridine **6** with an overall yield of 47% and 95% ee.

Scheme 1. Eight-Step Total Synthesis of Camptothecin from Known Pyridine **6**



In conclusion, reported herein is a concise total synthesis of camptothecin utilizing a mild and efficient cascade reaction followed by a highly enantioselective Sharpless dihydroxylation. This cascade sequence was efficiently triggered by bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate under mild conditions, and achieved significant enhancements in chemical yields.[12] Such a methodology

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(11) Chavan, S. P.; Venkatraman, M. S. *ARKIVOC* **2005**, 165−169.

(12) **Typical procedure for cascade reactions:** Trifluoromethanesulfonic anhydride (0.25 ml, 1.5 mmol) was added slowly to a solution of triphenylphosphane oxide (0.83 g, 3 mmol) in dry CH_2Cl_2 (15 mL) at 0 °C. After the mixture was stirred at 0 °C for 10 min, substrate **3** (1 mmol) was then added at the same temperature. The reaction was allowed to warm to room temperature and monitored by TLC (it usually completed after 1 h). The reaction mixture was quenched with 10% aqueous $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel to afford pure **4**.

should be particularly advantageous for preparing analogues that would be difficult to derive from natural camptothecin. It also offers the future possibility of developing an alternative industrial supply of CPT by chemical synthesis.

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Supporting Information Available: Experimental details and characterizations of new compounds, and copies of ^{1}H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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