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Short and Efficient Total Synthesis of Luotonin A and 22-Hydroxyacuminatine Using A Common Cascade Strategy

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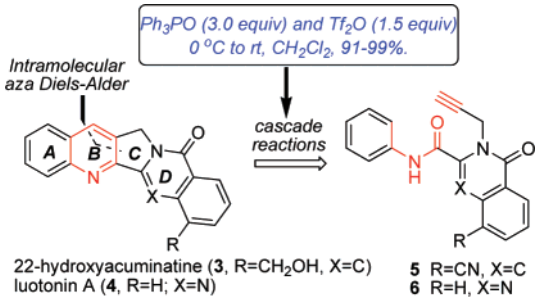

Total syntheses of 22-hydroxyacuminatine and luotonin A were achieved in direct fashion and high overall yields (16% in eight steps and 47% in five steps, respectively). A mild cascade methodology was successfully applied in both syntheses as a common strategy. The new approach presents the advantages of short routes, high overall yields, use of stable intermediates, and ease of operations.

The potent antitumor activities and clinical applications of camptothecin-family alkaloids have attracted intense interest worldwide. Their parent representative analogue, camptothecin (CPT, **1**), serves as an excellent lead drug in anticancer research because of its potent antitumor activity (Figure 1).[1] The primary cellular target of CPT and many CPT derivatives 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 (including clinically used anticancer drugs topotecan (**2a**)[3] and irinotecan (**2b**)[4] and some drug candidates[5] as well) have emerged from numerous research groups over the past decades.[6] 22-Hydroxyacuminatine (**3**) is another quinoline alkaloid isolated from Chinese medicinal plant (*Camptotheca acuminate*) (in a low isolated yield of 0.000006%) in 1989, showing significant cytotoxic activity against the murine leukemia P-388 cells (ED_{50} 1.32 μg/mL) and KB (ED_{50} 0.61 μg/mL) in vitro.[7] As the only natural alkaloid containing a benz[6,7]indolizino[1,2-*b*]quinolin-11(13*H*)-one core, 22-hydroxyacuminatine attracted lots of attention. Three total syntheses of 22-hydroxyacuminatine have been achieved.[8] Luotonin A (**4**) is one more CPT-family alkaloid isolated from another Chinese medicinal plant (*Peganum nigellastrum*) in 1997. Luotonin A also presents potent cytotoxicity against P-388 cells (IC_{50} 1.8 μg/mL).[9] Although it lacks the lactone functionality of CPT, luotonin A was recently demonstrated to stabilize the binary complex between human DNA and topoisomerase I and mediate topoisomerase I-dependent cytotoxicity in intact cells (IC_{50} 5.7−12.6 μM).[10] Several syntheses of luotonin A also have been reported.[11] Most importantly, Hecht and coworkers found that 14-azacamptothecin, a hybrid of luotonin A and CPT, is a water-soluble potent topoisomerase I poison.[12] Thus, further development of practical methods and general strategies for acquiring CPT-family alkaloids, including 22-

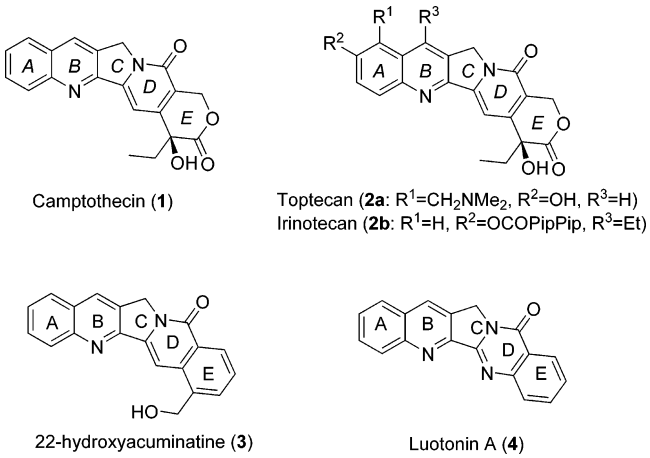

FIGURE 1. Structures of camptothecin (**1**), 22-hydroxyacuminatine (**3**), luotonin A, (**4**), and two representative drugs, **2a** and **2b**.

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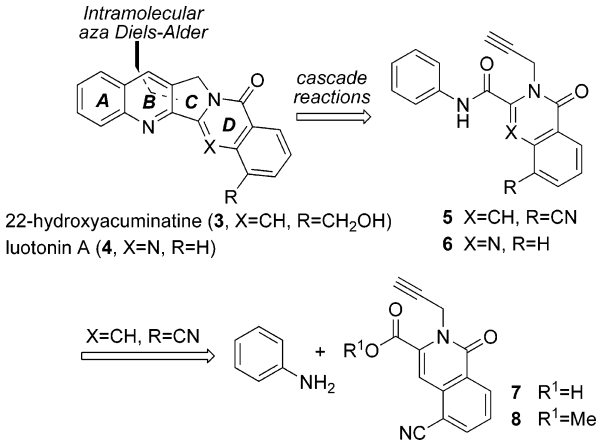


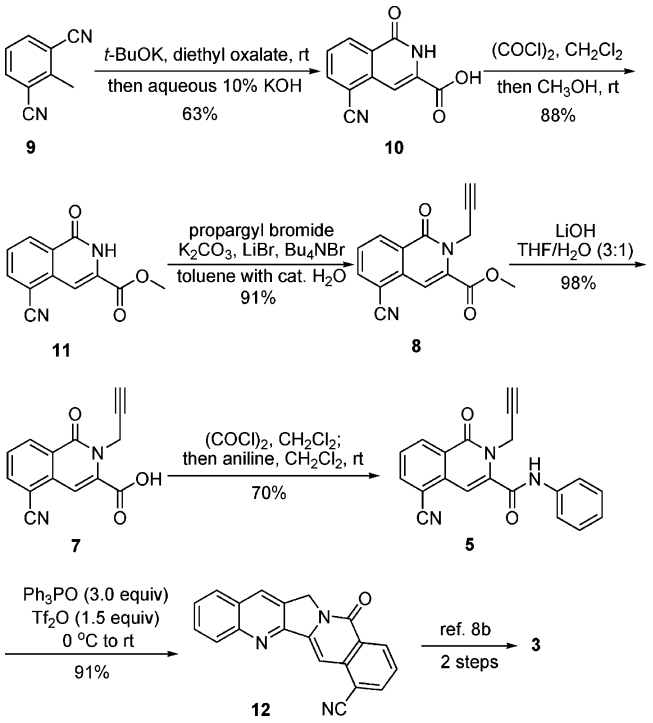
FIGURE 2. Retrosynthesis of 22-hydroxyacuminatine (**3**) and luotonin A (**4**) using a common cascade strategy.

hydroxyacuminatine (**3**), luotonin A (**4**), and other new CPT derivatives, is of great value.

More recently, we reported a mild cascade methodology to construct variously substituted indolizino[1,2-*b*]quinolin-9(11*H*)-ones, the tetracyclic A/B/C/D-ring core of CPT-family alkaloids.[6d,13] This highly efficient cascade reaction triggered by bis(triphenyl)-oxodiphosphonium trifluoromethanesulfonate under mild conditions has been successfully applied in total synthesis of camptothecin (**1**).[13] In order to examine the power of this methodology, two additional naturally occurring alkaloids, 22-hydroxyacuminatine (**3**) and luotonin A (**4**) were selected for its further applications. Both of them are notable with structural similarities to camptothecin (**1**) in identical A−C rings. Herein, we report our results of total syntheses of 22-hydroxyacuminatine (**3**) and luotonin A (**4**) using the above-mentioned cascade reaction as a common strategy. These two targets were successfully achieved in very short steps and high overall yields. Figure 2 illustrates their general retrosynthetic analysis. With the consideration of employing our cascade reaction conditions, chemically stable amides **5** and **6** have to be prepared at first, respectively.

Synthesis of 22-hydroxyacuminatine (**3**) started from the commercially available 2,6-dicyanotoluene **9** (Scheme 1).

SCHEME 1. Eight-Step Formal Total Synthesis of 22-Hydroxyacuminatine (3)



Condensation of 2,6-dicyanotoluene **9** with diethyl oxalate in the presence of potassium *tert*-butoxide, followed by a basic treatment, yielded 5-cyano-1-oxo-1,2-dihydroisoquinoline-3-carboxylic acid (**10**) in 63% yield.[14] Treatment of **10** with oxalyl chloride followed by reaction with excess methanol afforded ester **11** (88%). *N*-Propargylation of **11** was carried out with propargyl bromide, K_2CO_3, LiBr, and a catalytic amount of tetrabutylammonium bromide in toluene, giving a new pyridone **8** in 91% yield.[15] Basic hydrolysis of methyl ester **8** afforded acid **7** in 98% yield. Conversion of acid **7** to its corresponding acid chloride followed by treatment with aniline afforded amide **5** (70% yield in two steps). Amide precursor **5** was then treated with bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate (prepared in situ) at room temperature for half an hour.[13] The known advanced intermediate **12**[8b] was finally obtained (91% yield), containing the whole skeleton of 22-hydroxyacuminatine (**3**). Conversion of **12** to 22-hydroxyacuminatine (**3**) has been previously carried out by Cushman and co-workers using a two-step DIBAL-H reduction procedure (51% yield).[8b] Thus, using our mild cascade reaction, we accomplished a straightforward synthesis of the known key intermediate **12** (six steps and 31% yield) starting from commercially available 2,6-dicyanotoluene **9.** This represents a formal total synthesis of 22-hydroxyacuminatine (**3**) in eight steps and 16% overall yield.

Employing a similar strategy, total synthesis of luotonin A (**4**) was accomplished in five steps (Scheme 2). Reaction of the commercially available anthranilamide **13** with diethyl oxalate yielded a quinazolinone derivative **14** in 81% yield.[16] Ethyl ester **14** was then hydrolyzed with LiOH to give acid **15**.[17] Conversion

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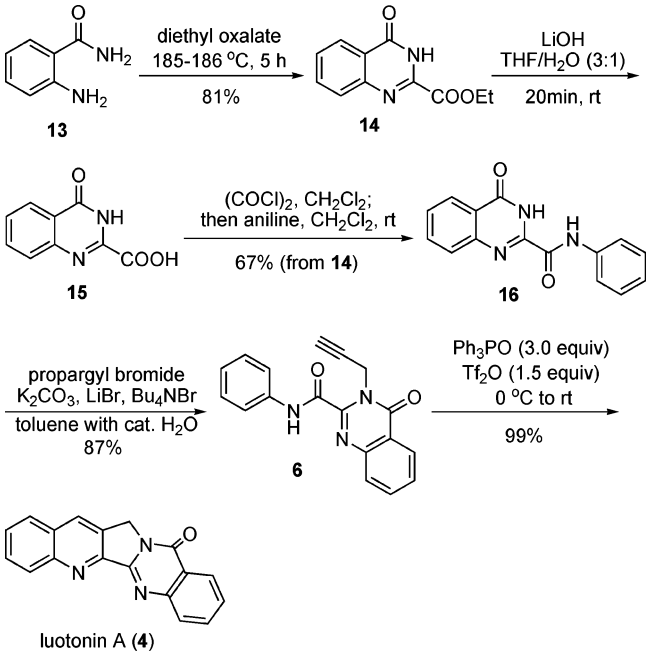
SCHEME 2. Five-Step Total Synthesis of Luotonin A



of **15** to its corresponding acid chloride, followed by coupling with aniline, afforded the amide **16** in 67% yield (from **14**). *N*-Alkylation of amide **16** with propargyl bromide provided the precursor amide **6** in 87% yield.[15] Finally, the cascade annulation was carried out by simple treatment of **6** with bis(triphenyl)-oxodiphosphonium trifluoromethanesulfonate at room temperature for 1 h, affording luotonin A (**4**) in 99% yield. This five-step synthesis of luotonin A represents an efficient overall yield of 47% from the commercially available **13**. To best of our knowledge, this is the shortest synthesis route for luotonin A. Compared with a similar strategy previously used by Batey and Twin,[11] our approach presents the advantages of a shorter route, higher overall yield (especially for the key cascade annulation step), and the use of the stable amide intermediate.

In conclusion, highly efficient and concise total syntheses of 22-hydroxyacuminatine and luotonin A were accomplished in direct fashions (eight steps and five steps, respectively) and high overall yields (16% and 47%, respectively). A mild and efficient cascade reaction was successfully employed as the common annulation strategy. Further applications of this useful and highly efficient cascade annulation protocol to construction of new CPT derivatives and other structurally related bioactive molecules are underway in our laboratory, and these results will be reported in due course.

Experimental Section

7-Cyano-12*H*-5,11a-diazadibenzo[*b*,*h*]fluoren-11-one (12).[8b] To a solution of triphenylphosphine oxide (0.77 g, 2.75 mmol) in dry CH_2Cl_2 (20 mL) was added trifluoromethanesulfonic anhydride (0.23 mL, 1.38 mmol) slowly at 0 °C. After the mixture was stirred at 0 °C for 10 min, amide **5** (0.30 g, 0.92 mmol) was then added at the same temperature. The reaction was allowed to warm to room temperature. After 0.5 h, the reaction mixture was quenched by addition of 10% aqueous $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2. 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 **12**[8b] (0.26 g, 91%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.77 (1H, d, J = 8.1 Hz), 8.40 (1H, s), 8.28 (1H, d, J = 8.4 Hz), 8.09 (1H, d, J = 7.5 Hz), 8.02 (1H, s), 7.94 (1H, d, J = 7.8 Hz), 7.85 (1H, t, J = 7.8 Hz), 7.67 (1H, t, J = 7.5 Hz), 7.63 (1H, t, J = 8.0 Hz), 5.41 (2H, s). HRMS (MALDI, *m*/*z*) calcd for $C_{20}H_{11}N_3O$ $(M+H)^+$: 310.0980; found, 310.0975. IR (KBr): 2229, 1664, 1637, 1591, 1550, 1473, 1394, 1377, 1296, 1253, 1205, 868, 816, 760, 705, 599 cm^{-1}. Anal. calcd for $C_{20}H_{11}N_3O$: C, 77.66; H, 3.58; N, 13.58; found: C, 77.65; H, 3.58; N, 13.57.

Luotonin A (4).[9,11] Compound **4** was prepared by a procedure similar to that for compound **12**, and it was isolated in 99% yield by column chromatography on silica gel (CH_2Cl_2/CH_3OH, 150:1 to 80:1) as a white solid; mp: 278−280 °C dec. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.46 (1H, d, J = 8.5 Hz), 8.43−8.40 (2H, m), 8.11 (1H, d, J = 8.1 Hz), 7.92 (1H, d, J = 8.1 Hz), 7.86 (1H, d, J = 8.2 Hz), 7.82 (1H, d, J = 8.2 Hz), 7.66 (1H, t, J = 7.5 Hz), 7.57 (1H, t, J = 7.5 Hz), 5.32 (2H, s). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.6, 152.6, 151.2, 149.5, 134.6, 131.5, 130.72, 130.68, 129.5, 128.8 (2C), 128.5, 127.9, 127.4, 126.4, 121.3, 47.3. IR (KBr): 1678, 1630, 1606, 1572, 1467, 1360, 1326, 1237, 769, 690, 604 cm^{-1}. HRMS (ESI, *m*/*z*) calcd for $C_{18}H_{12}N_3O$ $(M + H)^+$: 286.0975; found, 286.0990. Anal. calcd for $C_{18}H_{11}N_3O$: C, 75.78; H, 3.89; N, 14.73; found: C, 75.80; H, 4.10; N, 14.64.

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Supporting Information Available: Experimental details and characterization of new compounds, copies of NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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