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# Total synthesis of the cytotoxic alkaloid 22-hydroxyacuminatine

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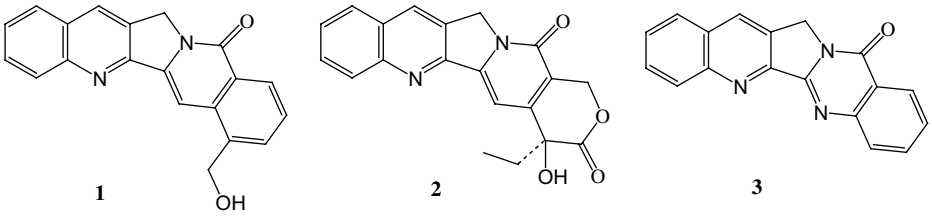
**Abstract**—The total synthesis of the cytotoxic alkaloid 22-hydroxyacuminatine has been achieved in 14.9% overall yield starting from 2-methylcinnamic acid via the key intermediate 5-ethoxymethylisoquinolin-1-one.


22-Hydroxyacuminatine (**1**) is a novel quinoline alkaloid isolated along with camptothecin (**2**) from *Camptotheca acuminate*.[1] It is the only known naturally occurring alkaloid containing the benz[6,7]indolizino[1,2-*b*]quinolin-11(13H)-one unit and showed potent cytotoxic activity against the P388 ($ED_{50}$ 1.32 μg/mL) and KB ($ED_{50}$ 0.61 μg/mL) cells in vitro.[1] Its pentacyclic ring structure closely resembles camptothecin (**2**) and luotonin A (**3**). Camptothecin (**2**) and its 10-OH analogues are well-known anti-cancer agents targeted at DNA topoisomerase I.[2–4] The key biochemical target for **2** is the covalent binary complex formed between DNA and topoisomerase I during DNA relaxation; stabilization of this complex by camptothecin is believed to lead to cell death.[3] Luotonin A (**3**) with a similar pentacyclic ring system also showed promising anti-cancer activity. In fact, we reported the first isolation of luotonin A (**3**), a pyrroloquinazolinoquinoline alkaloid, from *Peganum nigellastrum*[5] and demonstrated its cytotoxic and topoisomerase II inhibitory activities.[6] Recently, luotonin A (**3**) has been confirmed to stabilize the human DNA topoisomerase I/DNA covalent binary complex, affording the same pattern of cleavage as the structurally related camptothecin (**2**).[7] Because of the structural similarities among 22-hydroxyacuminatine (**1**), camptothecin (**2**) and luotonin A (**3**), notably in identical A–C rings, and their impressive anti-cancer activities, significant amount of efforts have been directed toward the total synthesis of such pentacyclic alkaloids. As a result, novel synthetic routes to camptothecin (**2**) and luotonin A (**3**) have been developed and generated several highly promising analogues.[8,9] Unexpectedly, the synthesis of 22-hydroxyacuminatine (**1**) has not been reported yet. Therefore, in conjunction with synthetic efforts, herein we report the first total synthesis of 22-hydroxyacuminatine (**1**) as shown in Scheme 1.

Reaction of starting material 2-methylcinnamic acid (**4**) with thionyl chloride and ethanol gave the ester **5** in 93% yield. Bromination of **5** with N-bromosuccinimide in the presence of 2,2-azobisisobutyronitrile under reflux for 2 h, followed by etherification with ethanol gave the ether **6** (62% yield). Hydrolysis of **6** with potassium hydroxide in a water–acetone solution at room temperature afforded the acid **7** in 96% yield. The 2-ethoxymethylcinnamic acid (**7**) was converted to the key

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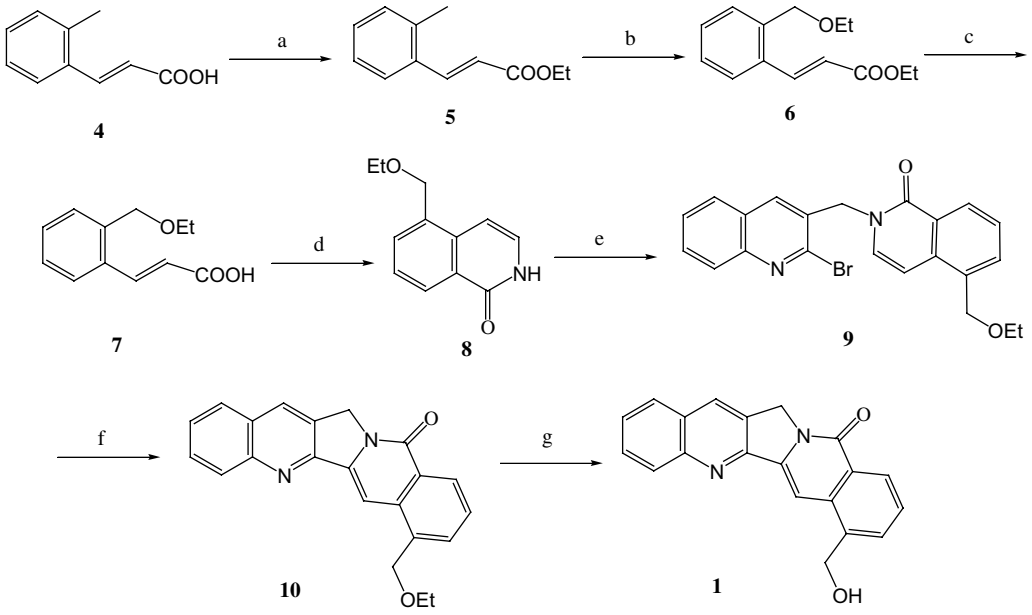


**Scheme 1.** Reagents and conditions: (a) (1) $SOCl_2$, $CH_2Cl_2$, reflux, 2 h; (2) EtOH, $Et_3N$, rt, overnight; (b) (1) NBS, AIBN, $CCl_4$, reflux, 2 h; (2) EtOH, NaOEt, rt, 6 h; (c) 0.5 N KOH solution, acetone, rt, overnight; (d) (1) $SOCl_2$, $CH_2Cl_2$, reflux, 2 h; (2) $NaN_3$, 1,4-dioxane/water (1:1), 0 °C, 1 h; (3) $Ph_2O$, $Bu_3N$, 230 °C, 1 h; (e) 2-bromo-3-(bromomethyl)quinoline, *t*-BuOK, DMF, rt, 2 h; (f) $Pd(OAc)_2$, KOAc, $Cy_3P$, DMF, reflux, 0.5 h; (g) (1) $BBr_3$, $CH_2Cl_2$, −78 °C to rt; (2) $AgNO_3$, aq acetone, reflux, 3 h.

intermediate 5-ethoxymethylisoquinolin-1-one (**8**) according to slightly modified literature procedures in 52% yield.[10] N-alkylation of **8** with 2-bromo-3-(bromomethyl)quinoline[11] in the presence of potassium *tert*-butoxide gave **9** in 71% yield. The Heck reaction[9j,12] was used to convert **9** to the ether analogue of 22-hydroxyacuminatine (**10**, 96% yield). Cleavage of the ethyl ether with excess boron tribromide in methylene chloride, followed by solvolysis with silver nitrate in aqueous acetone gave 22-hydroxyacuminatine (**1**) in 76% yield. The spectral data of **1** were in agreement with authentic sample reported in the original paper.[1,13]

In conclusion, the total synthesis of 22-hydroxyacuminatine (**1**), an important member of a class of naturally occurring pentacyclic alkaloids, has been achieved in seven steps by using commercially available 2-methylcinnamic acid as starting material in a total yield of 14.9%. The synthesis of additional analogues for evaluating their anti-cancer activity is in progress and will be reported shortly.

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13. Spectral data for **1**: $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 4.95 (d, $J$ = 4.8 Hz, 2H), 5.35 (s, 2H), 5.51 (t, $J$ = 4.8 Hz, 1H), 7.56 (t, $J$ = 7.8 Hz, 1H), 7.68 (dt, $J$ = 1.5 and 7.5 Hz, 1H),

7.71 (s, 1H), 7.80 (d, $J$ = 7.5 Hz, 1H), 7.85 (dt, $J$ = 1.5 and 7.8 Hz, 1H), 8.10 (d, $J$ = 8.1 Hz, 1H), 8.19 (d, $J$ = 8.4 Hz, 1H), 8.29 (d, $J$ = 7.8 Hz, 1H), 8.64 (s, 1H); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) $\delta$ 49.5, 61.2, 96.2, 125.8, 125.9, 126.7, 127.3, 127.9, 128.4, 128.8, 129.7, 130.2, 131.1, 131.3, 135.2, 138.5, 140.1, 148.0, 153.3, 159.9; ESI MS $m/z$ 315 $(M + H)^+$; HR ESI MS $m/z$ 315.1136 [$(M + H)^+$, $C_{20}H_{15}N_2O_2$, requires 315.1133].