A Concise and Convergent Synthesis of Luotonin B and E

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Abstract: A concise and highly convergent practical synthesis of topoisomerase 1 inhibitor luotonin B was developed in a one-pot process in excellent yields. The C and D rings of luotonin B was constructed by cascade cyclizations of 2-cyanoquinoline-3-aldehyde or 2-cyanoquinoline-3-hemiacetal with methylanthranilate under acidic conditions. The luotonin B was then converted into luotonin E by an acid-catalyzed etherification reaction.

Key words: luotonin A, B and E alkaloids, camptothecin, 2-cyanoquinoline-3-aldehyde, 2-cyanoquinoline-3-acetal, methyl anthranilate, cascade cyclization

The pyrrolo[3,4-*b*]quinoline ring system is found in a wide range of pharmacologically significant compounds and in some bioactive natural products, exemplified by topoisomerase I inhibitors luotonin A (**1**), B (**2**), E (**3**), and camptothecin (**4**, Figure 1).[1] Luotonin A, B, and E were isolated in 1977 from aerial parts of *Peganum nigellastrum* Bunge, a Chinese medicinal plant used for treatment of rheumatism, inflammation, abscesses, and other maladies. Luotonin alkaloids possess a unique structural array comprising of pharmacologically important quinoline[2] and quinazoline[3] ring systems. Among these pyrrolo[3,4-*b*]quinoline alkaloids, luotonin A is a human DNA topoisomerase 1 inhibitor, and exhibits remarkable cytotoxicity toward murine leukemia P388 cell line at low concentrations (IC 50 1.8 μg/mL) by stabilizing the topoisomerase 1 and DNA complex.[4] Luotonin A is reminiscent of camptothecin (CPT), a novel pentacyclic alkaloid which displays significant activity against mice leukemia L1210 and Walker 256 sarcoma in rats.[5] The biological properties of luotonin and camptothecin derivatives[6] have prompted a flurry of synthetic activity in recent times that has culminated in several impressive total syntheses of these alkaloids.

Several synthetic approaches have been developed for the total synthesis of luotonin A (**1**), B (**2**), and E (**3**) alkaloids. The radical cyclization of *N*-acylcynamide,[7] intermolecular and intramolecular hetero Diels–Alder (Povarov) reaction,[8] sequential A, B, C, D, and E ring construction strategy,[9] cascade approach,[10] Friedländer–Friedländer, and Borsche chemistry[11] are some of the noteworthy synthetic methodologies employed in the total synthesis of luotonin alkaloids. However, involvement of difficult operations and complex starting materials makes most of these syntheses impractical. We herein present a novel cascade, and highly convergent synthesis of luotonin B and E alkaloids.

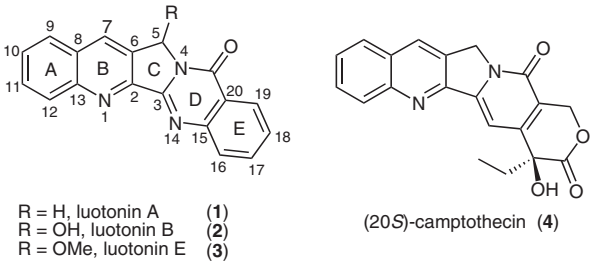
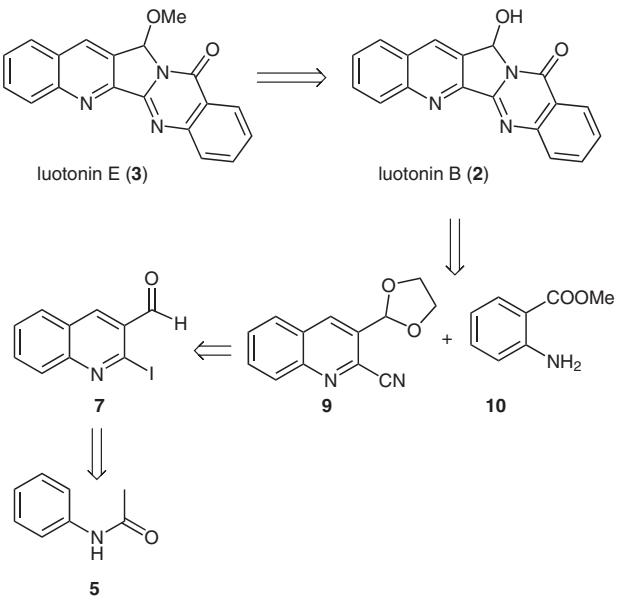


Figure 1

We were intrigued by the possibility of luotonin B (**2**) and E (**3**) alkaloid synthesis by short and efficient approach as shown in our retrosynthetic analysis (Scheme 1). The basic synthetic design of our disconnection approach features the reaction of 3-(1,3-dioxalan-2-yl)-2-cyanoquinoline (**9**) with methyl anthranilate (**10**) and subsequent cascade cyclization to construct luotonin B (**2**) in a one-pot process. Luotonin B (**2**) could then etherify under mild conditions leading to the formation of luotonin E (**3**). This modular approach should also provide a convenient method for analogue synthesis.



Scheme 1

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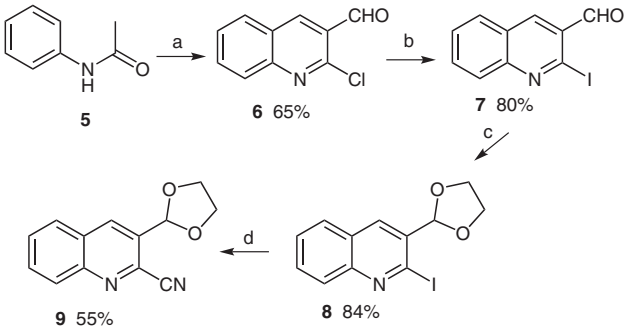
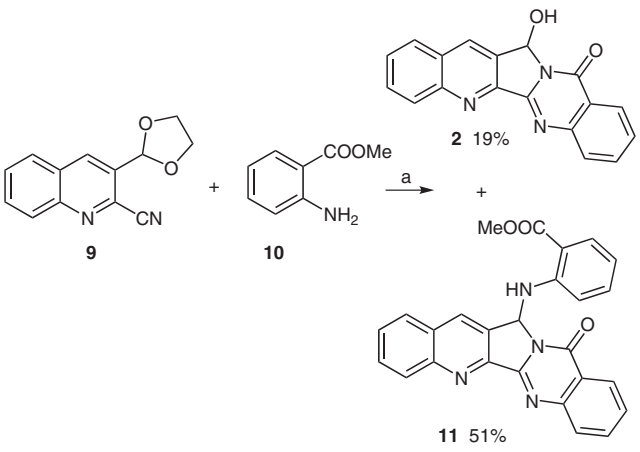
The 3-(1,3-dioxalan-2-yl)-2-cyanoquinoline (**9**) required for luotonin synthesis was prepared from Meth-Cohn's 2-chloro-3-quinoline-3-aldehyde[12] (**6**) in excellent overall yields, as shown in Scheme 2. The 2-chloro-3-quinoline-3-aldehyde (**6**) was converted into iodo derivative[13] **7** as per the literature reports. Acetal protection of **7** followed by cyanation[14] afforded **9** in overall 54% yield.



Scheme 2 *Reagents and conditions*: (a) DMF, $POCl_3$, 70–80 °C; (b) NaI, HCl (cat.), MeCN, 80–90 °C; (c) ethylene glycol, PTSA; (d) CuCN, TBAB, MeCN, 80–90 °C.

Our initial attempts to react 3-(1,3-dioxalane-2-yl)-2-cyanoquinoline (**9**) with methyl anthranilate (**10**) under basic reaction conditions were not successful. The reaction was also attempted with mild Lewis acids in various polar protic and aprotic solvents, but no characterizable product could be isolated from the reaction mixture under these conditions. However, when the reaction was performed in acetic acid under reflux conditions for about 12–16 hours, direct precipitation of luotonin B (**2**) in the reaction mixture along with anthranilate-substituted luotonin B **11** were observed (Scheme 3).[15] The precipitated product mixture was filtered at room temperature and purified by column chromatography. The luotonin B was isolated in 19% yield as an off-white solid, and **11** was isolated in 54% yield. The ^1H and ^{13}C NMR data and the melting point of the synthetic luotonin B were found to be identical to the reported data. Despite various attempts to



Scheme 3 *Reagents and conditions*: (a) AcOH, 110 °C, 12 h.

improve the formation of **2** under these conditions by the reaction of 3-(1,3-dioxalan-2-yl)-2-cyanoquinoline (**9**) and methyl anthranilate (**10**), the yield remained low.

The above reaction is assumed to proceed through intermediates **12** and **13** by a preferential pyrimidone D ring formation. The pyrimidone **13** on acetal cleavage results in either pyrimidoaldehyde **14** or pyrimidoimine **15** (Figure 2). The C ring formation through intermediate **14** yields **2** and cyclization through imine **15** results in **11**.

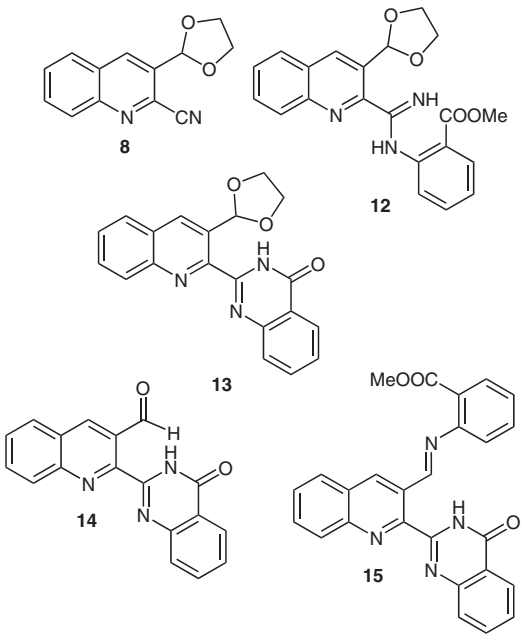
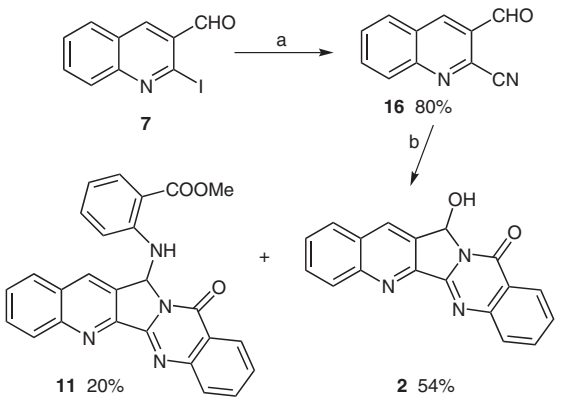


Figure 2

In order to improve the yield of the reaction, various options were investigated, and the reaction was performed with cyanoaldehyde **16** and anthranilate **10** (Scheme 4). The cyanoaldehyde **16** required for the synthesis was prepared by the reaction of **7** with copper(I) cyanide in acetonitrile at 80–90 °C. The synthesis of luotonin B (**2**) was performed in acetic acid in presence of substoichiometric quantity of acetic anhydride under reflux conditions, and crude luotonin B was directly precipitated out from the reaction mixture along with **11**.[16,17] The mother liquor was then diluted with water, and extracted with ethyl acetate. The precipitated product mixture and the ethyl acetate extracts were combined together and purified by column chromatography. Luotonin B (**2**)[18] was isolated in 54% yield while **11** was isolated in 20% yield.

The reaction proceeds through intermediates **15** or **17**. Since the cyanoaldehyde **16** is more reactive, the formation of pyrrolo[*c*]quinoline **17** could occur much faster than pyrimidoimine **15**. Pyrrolo[*c*]quinoline **17** on intramolecular cyclization affords luotonin B (**2**) through D ring formation (Figure 3).

The luotonin B (**2**) was then converted into luotonin E (**3**) under acid-catalyzed etherification. Though initially the reaction was performed with PTSA/MeOH in almost



Scheme 4 *Reagents and conditions*: (a) CuCN, TBAB, MeCN; (b) **10** (1.05 equiv), AcOH, Ac_2O.

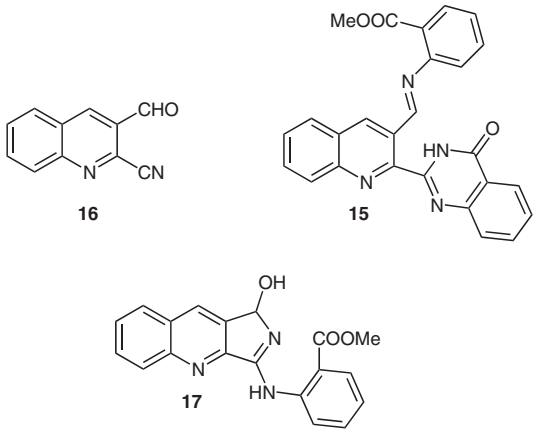
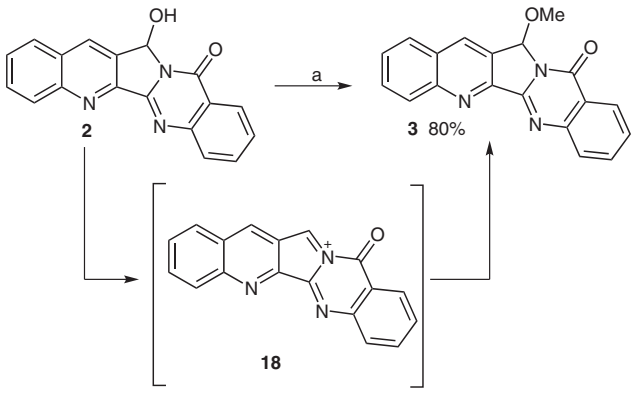


Figure 3



Scheme 5 *Reagents and conditions*: MeOH, Amberlyst or MeOH, Indion resin, 60 °C.

quantitative yield, the reaction also worked equally well with Amberlyst 25 acidic resin as well as with Indion resin.[19]

We assume the etherification reaction occurs through iminium ion **18** under acidic conditions. Iminium ion **18** is then trapped by methanol present in the reaction medium, leading to the formation of **3** (Scheme 5). This methodology may help to generate a series of new luotonin derivatives for biological evaluation.

We also attempted the conversion of luotonin B (**2**) into luotonin A (**1**) under acid-catalyzed reduction conditions. However, our attempted reduction of **2** with various reducing agents such as $NaBH_4$, $LiBH_4$, etc. did not yield the expected product. Interestingly, the mesyl-protected lutonin B **19** when subjected to hydrogenation under Pd/C conditions, **20**[20] was isolated as the major product by the partial reduction of luotonin B and D rings (Scheme 6).

In summary, a highly convergent cascade process has been developed for the synthesis of luotonin B in excellent yield in a one-pot operation. The novel synthetic approach involves assembling the C and D rings of luotonin B in the presence of acetic acid using easily synthesized starting materials. This novel methodology appears to be well suited to preparation of simple congeners and several analogues that may prove useful in defining a pharmacological profile of this class of luotonin alkaloids and their derivatives. We are further exploring the application of this cascade reaction sequence for the synthesis of other naturally occurring compounds having pyrroloquinazolinoquinoline or related structural features which will be published in due course. Also as a part of this work, luotonin E was synthesized by etherification of luotonin B under acidic conditions in methanol.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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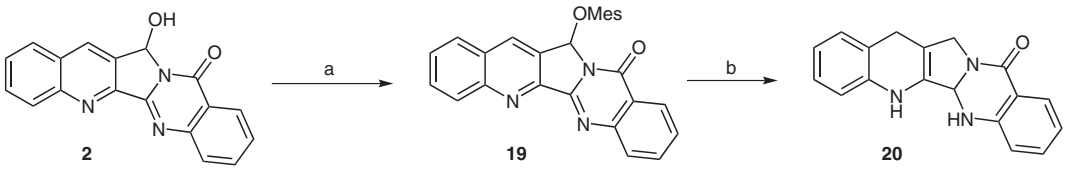

Scheme 6 *Reagents and conditions*: MesCl, Et_3N, CH_2Cl_2; (b) Pd/C (10%), MeOH.

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(15) To a suspension of 2-cyanoquinoline-3-acetal (**9**, 1 g, 0.004 mol, 1 equiv) in AcOH (10 mL), methyl anthranilate (0.7 g, 0.005 mol, 1.05 equiv) was added, and the reaction mixture was heated to reflux for a period of 12–14 h. The reaction mass was then cooled, the precipitated product was filtered off, and further purified by column chromatography using EtOAc and hexane (7:3) to yield the lutonin B. The filtrate was diluted with H_2O, and extracted with EtOAc, and dried. Concentration and purification by column chromatography yielded **11**.
(16) To a suspension of cyanoaldehyde (1 g, 0.5 mmol, 1 equiv) in AcOH (10 mL) and Ac_2O (0.2 mL), methyl anthranilate (0.554 g, 0.71 mmol, 1.5 equiv) was added, and the reaction mixture was heated to reflux for a period of 12–14 h. The reaction mass was then cooled to r.t., and precipitated product was filtered off. The mother liquor was then diluted with H_2O, and extracted with EtOAc. The precipitated product mixture and the EtOAc extracts were combined together, concentrated under vacuum. The product was then purified by column chromatography using EtOAc and hexane (7:3), and pure luotonin B was isolated as white to off-white solid in 0.890 g, 54% of yield. Also 12% of **11** was also isolated from the column.
(17) **Methyl-2-(11-oxo-11,13-dihydroquinolino[2′,3′:3,4]-pyrrolo[2,1-*b*]quinazolin-13-yl)amino benzoate (11)**
Yield 20%; mp 312–314 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.80 (s, 3 H), 6.77 (t, *J* = 7.2 Hz, 1 H), 7.26 (s, 1 H), 7.27 (s, 1 H), 7.35 (t, *J* = 7.6 Hz, 1 H), 7.52 (t, *J* = 6.8 Hz, 1 H), 7.69 (t, *J* = 7.6 Hz, 1 H), 7.80–7.97 (m, 4 H), 8.1 (d, *J* = 8.0 Hz, 1 H), 8.34 (dd, *J* = 1.6, 7.8 Hz, 1 H), 8.48 (s, 1 H) 8.52 (d, *J* = 8.8 Hz, 1 H), 8.85 (d, *J* = 9.6 Hz, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 51.8, 68.4, 112, 113.6, 117.6, 122.4, 126.7, 127.6, 128.4, 128.6, 128.8, 129.1, 130.8, 131.2, 131.7, 132.2, 132.6, 134.4, 134.6, 148.0, 149.0, 150.0, 150.4, 151.4, 160.6, 168.9. MS: *m/z* (%) = 435 [M + 1], 302.2, 137.1. Anal Calcd for $C_{26}H_{18}N_4O_3$: C, 71.88; H, 4.18; N, 12.90. Found: C, 71.86; H, 4.15; N, 12.87.
(18) Luotonin B (**2**)
Yield 0.89 g (54%); mp 273–275 °C. IR (KBr): 1028, 1266, 1449, 2041, 2945, cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.98 (d, *J* = 8.4 Hz, 1 H), 7.62–7.66 (m, 2 H), 7.78 (t, *J* = 7.2 Hz, 1 H), 7.92–7.96 (m, 3 H), 8.23 (d, *J* = 8.0 Hz, 1 H), 8.28 (dd, *J* = 3.6 Hz, 8.4 Hz, 2 H), 8.80 (s, 1 H). ^{13}C NMR (400 MHz, DMSO-d_6): δ = 80.5, 122.2, 126.1, 127.5, 128.2, 128.3, 128.7, 128.8, 129.6, 131.0, 132.8, 133.8, 134.7, 148.7, 149.1, 150.3, 151.5, 159.4. MS *m/z* (%) = 302.1 [M + 1], 246.2, 150.1. Anal Calcd for $C_{18}H_{11}N_3O_2$: C, 71.75; H, 3.68; N, 13.95. Found: C, 71.77; H, 3.69; N, 13.90.
(19) To a solution of luotonin B (0.35 g, 0.16 mol, 1 equiv) in MeOH (3.5 mL, 10 V), Indion resin (0.1 g, 0.01 mmol, 0.1 equiv) was added, and the reaction mixture was heated at 55 °C for a period of 6–7 h. The reaction mixture was then cooled, and the resin was filtered off and washed with MeOH (1 mL). The filtrate was concentrated under reduced pressure, and purified on a filter column using EtOAc–hexane (30:70). The product was isolated as a white to off-white solid in 80% (0.29 g) yield.
Luotonin E
Yield 0.29 g (80%).; mp 222–224 °C. IR (KBr): 1047, 1237, 1300, 1375, 1730, 2985 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.60 (s, 3 H), 6.90 (s, 1 H), 7.58 (dt, *J* = 0.8, 7.6, 11.2 Hz, 1 H), 7.71 (t, *J* = 6.8 Hz, 1 H), 7.82–7.88 (m, 2 H), 7.99 (d, *J* = 8.4 Hz, 1 H), 8.09 (d, *J* = 8.0 Hz, 1 H) 8.41 (dd, *J* = 1.2, 8.0 Hz, 1 H), 8.47 (d, *J* = 8.4 Hz, 1 H), 8.5 (s, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 56.3, 87.0, 122.2, 126.8, 127.8, 128.4, 128.6, 128.8, 130.0, 130.7, 131.3, 133.0, 134.8, 148.9, 150.4, 151.3, 160.7. MS: m/z (%) = 316.2 [M + 1],

279.2, 130.2. Anal Calcd for $C_{19}H_{13}N_3O_2$: C, 72.37; H, 4.16; N, 13.33. Found: C, 72.34; H, 4.15; N, 13.35.

(20) **Tetrahydroluotonin A (20)**
Yield 190 mg (50%); mp 191–193 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.57 (dd, *J* = 8.0, 14.8 Hz, 1 H), 2.95–3.06 (m, 2 H), 4.03 (dd, *J* = 4.0, 12.0 Hz, 1 H), 4.33 (dd, *J* = 6.8, 12 Hz, 1 H), 4.66 (s, 1 H), 4.81 (dd, *J* = 3.2, 7.8 Hz, 1 H), 6.65 (d, *J* = 6.7 Hz, 1 H), 6.70 (dd, *J* = 0.4, 10.6 Hz, 1 H), 7.01 (m, 2 H) 7.45 (m, 1 H), 7.72–7.80 (m, 2 H), 8.29 (d, *J* = 8.4 Hz, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 28.5, 31.6, 49.7, 57.6, 114.3, 118.6, 120.0, 121.1, 126.4, 126.7, 127.1, 127.6, 128.8, 134.2, 142.6, 149.2, 159.5, 160.9. MS: *m/z* (%) = 435 [M + 1], 290.2, 202.2, 186.2. Anal Calcd for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52. Found: C, 74.70; H, 5.21; N, 14.57.