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Total Synthesis of Camptothecin and SN-38

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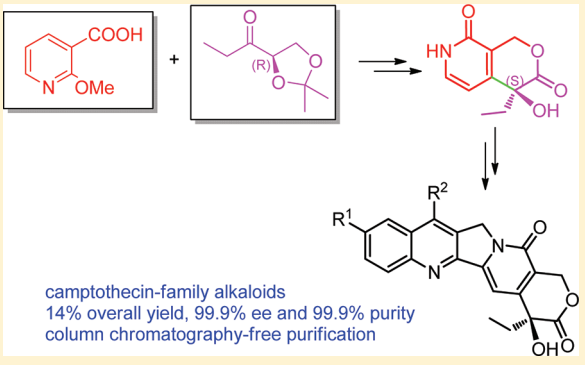
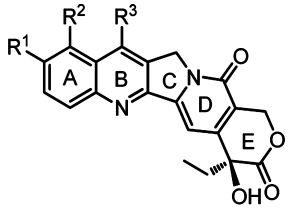
Supporting Information

ABSTRACT: A new practical and concise total synthesis of enantiopure camptothecin and SN-38 (14% overall yield, 99.9% ee and 99.9% purity) was described, starting from inexpensive and readily available materials. The development of column chromatography-free purification was achieved in all steps, which offers an economic industrial process to the camptothecin-family alkaloids.



Camptothecin (CPT **1**, Figure 1) was first isolated from *Camptothecin acuminata* by Wani and Wall in 1966.[1] This



camptothecin (1 R^1=R^2=R^3=H)
topotecan (2 R^1=OH,R^2=CH_2NMe_2.HCl,R^3=H)
irinotecan (3 R^1=OCOPipPip,R^2=H,R^3=Et)
SN38 (4 R^1=OH,R^2=H,R^3=Et)

Figure 1. Camptothecin and two representative derivatives.

natural alkaloid showed potent antitumor activity and a unique mechanism of action, which selectively inhibits DNA topoisomerase I (Topo I), thus attracting intense interest worldwide as a prominent lead for the development of new anticancer drugs.[2−5] For its good antitumor profiles and unique mechanism, an amount of camptothecin analogues have been synthesized and investigated to find better camptothecin derivatives with reduced toxicity and improved anticancer activity. To date, two camptothecin analogues, topotecan (**2**)[6] and irinotecan (**3**),[7] have been approved by the FDA to treat cancers, among which irinotecan (**3**) turned out to be a more active metabolite SN-38 (**4**)[8] in vivo. In addition, several others, such as BNP-1350, silatecan, ST-1481, lurtotecan, and diflomotecan, are presently in different stages of preclinical and clinical trials.[9]

Since the common drawback of industrial-scale extraction from the medical plants, development of practical and concise total synthesis of CPT-family alkaloids has attracted the interest of both organic and medicinal scientists over the past decades.[10] As summarized in Du's review in 2003,[10] the major synthetic approaches are roughly classified as the C-ring construction approach, the cascade radical cyclization approach, the broadly applied Friedlander condensation approach, various Michael addition approaches, and various Diels−Alder reaction approaches. Recently, many impressive total syntheses of camptothecins have been developed in numerous research groups,[11−24] which dramatically advanced the development of organic synthesis and anticancer medicinal chemistry. Despite exhaustive attempts to develop a practical synthesis, most approaches still suffered from infeasibility of column chromatography, low yields, high cost, or toxic reagents. Among these reported total synthesis strategies, Comins' method was an efficient route to construct the key core of CPT-family alkaloids by coupling the A/B ring with the D/E ring,[25−28] but employment of expensive reagents made this approach unpreferable for application in the industry. In Comins' approach, the chiral center of compound **5** was obtained by the stereoselectively nucleophlic addition of 2-ketobutyric acid ester with expensively chiral auxiliaries in only 93% ee value.[29] Recently, we disclosed a short and efficient route for producing racemic compound **5**,[30] in which 2-chloronicotinic acid was employed as the starting material (Figure 2). Based on this previous work, we present a scalable and concise total synthesis of camptothecin (**1**) and SN-38 (**4**) starting from inexpensive and readily available materials.

According to our retrosynthesis shown in Figure 2, ring C was constructed through joining of the A/B ring and the D/E ring (**5**) based on our previous work.[30] It was obvious that

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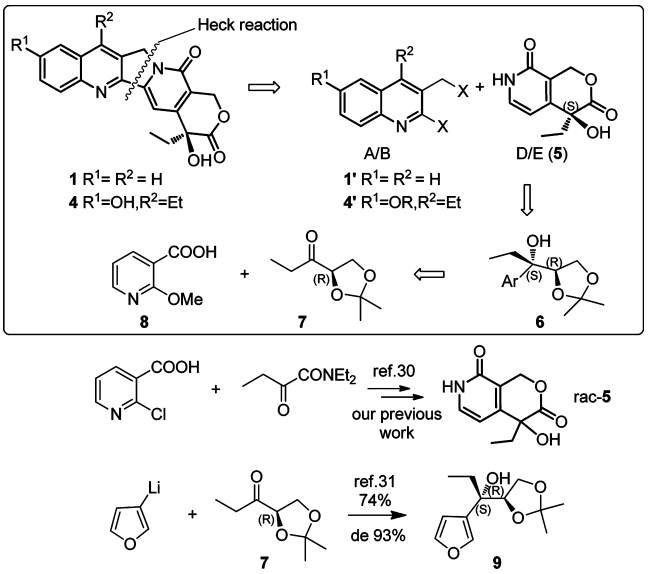


Figure 2. Retrosynthesis of camptothecin (**1**) and SN-38 (**4**).

asymmetric alcohol **6** was the key fragment in this work. In 2002, Wong's group[31] reported that this *S*-configuration tertiary alcohol (**9**) was constructed by a nucleophilic addition of lithiated furan and glyceraldehyde derivative (**7**) in yield of 74% and de value of 93%, which inspired us that this chiral moiety could be further converted into the key scaffold, a tertiary alcohol acid.

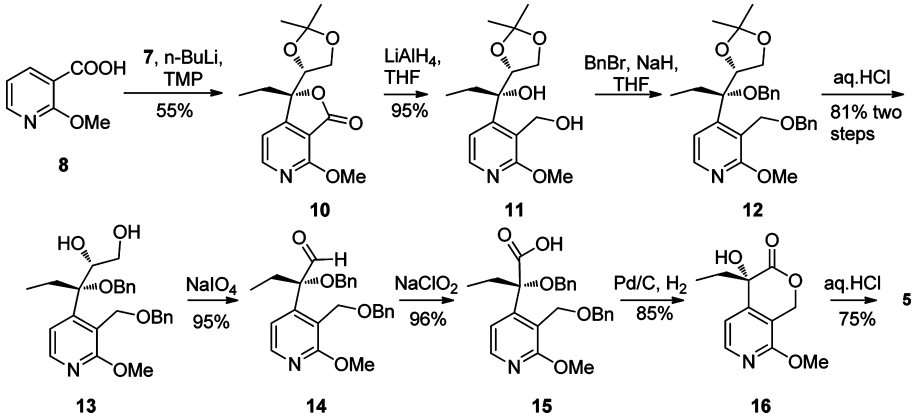
Thus, the DE ring (**5**) was prepared as outlined in Scheme 1. To facilitate the formation of pyridone (**5**) in the final step, commercially available 2-methoxynicotinic acid (**8**) was chosen as the starting material, which was lithiated with LTMP (3 equiv compared to **8**) and subsequently subjected to a nucleophilic addition with chiral ketone **7**[32] (3 equiv compared to **8**) at −60 to −78 °C to afford lactone **10** in a yield of 55%. Fortunately, this lactone **10** could be recrystallized right from the reaction solution in extraordinarily high purity (chemical purity >99.9%, de value >99.9%), and its diastereoisomer was not detected in the LC−MS system. The key intermediate **10** was thus subjected to X-ray crystallography, which confirmed that the chiral center was the desired *S*-configuration (Figure 3, see the Supporting Information). Later, we tried to optimize the reaction conditions in this step, the molar ratio of compound **7** to **8** was first reduced to 2:1 from 3:1, but the yield was very low. Then, replacing LTMP with LDA or reducing the amount of n-BuLi also decreased the yield dramatically. Finally, warming the temperature to higher than −60 °C made the reaction more complex. As all these attempts were unsuccessful, the aforementioned conditions were thus considered as the preferred conditions as follows: LTMP was better than LDA, the molar ratio of compound **8** to **7** should be 1:3, and the temperature should be lower than −60 °C.

Then, compound **10** was reduced with $LiAlH_4$ to give diol **11** in 95% yield. Subsequently, the two hydroxyl groups in **11** were protected with benzyl to afford **12**, which was then hydrolyzed under acidic condition to give glycol **13** in an excellent yield. Glycol **13** was subjected to sequent oxidative cleavage and oxidation to produce acid **15**. Hydrogenation proceeded smoothly to remove the benzyl groups and resulted in ring-closing product **16**, which was hydrolyzed under acidic conditions to give D/E fragment **5** with >99.5% purity and >99.8% ee value. The total yield of these eight steps was 25%.

With the key intermediate **5** in hand, CPT-family alkaloids can be obtained by using condensation and Heck reaction with different A/B fragment.[33−36] Here, synthesis of SN-38 (**4**) as an example is shown in Scheme 2. Compound **17** was synthesized by a general procedure which was similar as the synthesis of unsubstituted A/B ring,[33,34] starting from **17a**.[37] The condensation of **5** and **17** under basic conditions gave intermediate **18**, which was subjected to Heck reaction to produce **19**. Deprotection of **19** afforded SN-38 (**4**) in excellent yield. In addition, camptothecin (**1**) and 10-hydroxycamptothecin were also prepared in this way, and the purity and ee value for all these CPT-family alkaloids exceeded 99.9% without column chromatography in all steps. The data for these synthesized camptothecins were in good agreement with those of natural products.

In summary, we have succeeded in implementing a practical and concise total synthesis of camptothecin (**1**) and SN-38 (11 steps, 14% overall yield, 99.9% ee, and 99.9% purity), employing an inexpensive and commercial available material (**8**) as starting material and compound **7** as asymmetric inducing reagent. It is worth mentioning that the development of column chromatography-free purification was achieved in all steps, which will be valuable as an economical industrial process of producing camptothecin-family alkaloids.

Scheme 1



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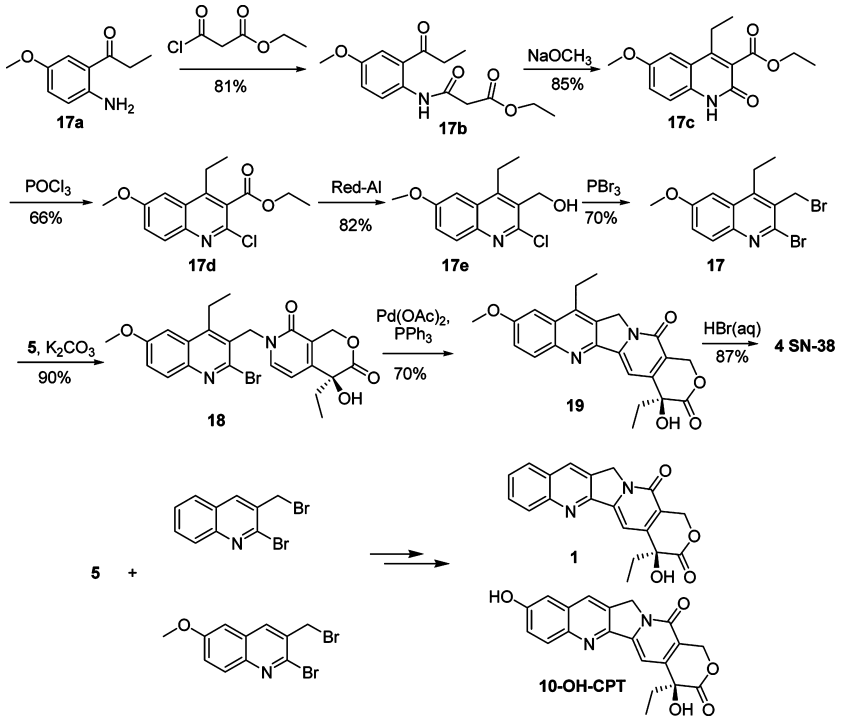
Scheme 2



EXPERIMENTAL SECTION

(*S*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-1-ethyl-4-methoxyfuro[3,4-*c*]pyridin-3(1*H*)-one (10). *n*-BuLi (58.5 mL, 2.5 M in *n*-hexane) was added to a solution of 2,2,6,6-tetramethylpiperidine (14.4 mL, 117.6 mmol) in anhydrous THF (200 mL) at −78 °C under nitrogen. The mixture was stirred for 30 min before 2-methoxynicotinic acid (**8**, 4.84 g, 31.64 mmol) was added. After the mixture was stirred for 30 min at −78 °C, compound **7** (15.0 g, 94.9 mmol) was added and and the mixture stirred for another 30 min. Then the mixture was allowed to reach room temperature and hydrolyzed with 1 N HCl (50 mL). The mixture was extracted with ethyl acetate, dried over anhydrous Na_2SO_4, and concentrated to afford 25.0 g of crude **10**, which was further purified by trituration with petroleun ether (20 mL) to give pure **10** as a white solid (4.7 g, 55% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.64 (t, J = 7.5 Hz, 3H), 1.30 (s, 3H), 1.42(s, 3H), 2.06 (m, 1H), 2.22 (m, 1H), 4.04 (m, 2H), 4.14 (s, 3H), 4.16 (m, 1H), 7.04 (d, J = 5.5 Hz, 1H), 8.40 (d, J = 5.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.6, 24.5, 24.6, 25.8, 54.3, 64.8, 78.5, 88.2, 109.1, 110.4, 111.0, 152.9, 161.4, 163.4, 167.0; MS (EI) m/z = 293; HRMS (EI) m/z calcd for $C_{15}H_{19}NO_5$ $[M]^+$ 293.1263, found 293.1264.

(*S*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-1-(3-(hydroxymethyl)-2-methoxypyridin-4-yl)propan-1-ol (11). A solution of the compound **10** (5.5 g, 19 mmol) in anhydrous THF (50 mL) was added slowly to a mixture of $LiAlH_4$ (1.3 g, 34 mmol) in anhydrous THF (30 mL), and then the mixture was stirred for 2 h at the room temperature, cooled to 0 °C, and quenched with water (2.5 mL). The mixture was filtered, extracted with ethyl acetate, dried over anhydrous Na_2SO_4, and evaporated to dryness to give a white solid **11** (5.4 g, 95.0% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.78 (t, J = 7.4 Hz, 3H), 1.40 (s, 3H), 1.48 (s, 3H), 2.00 (m, 1H), 2.97 (s, 1H), 3.26 (s, 1H), 3.58 (m, 1H), 3.73 (m, 1H), 3.97 (s, 3H), 4.55 (m, 1H), 4.89 (m, 2H), 6.72 (d, J = 5.5 Hz, 1H), 8.02 (d, J = 5.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.7, 25.0, 26.2, 24.1, 53.8, 56.4, 65.5, 78.2, 80.2, 110.0, 114.8, 121.7, 145.4, 150.3, 163.3; MS (EI) m/z = 297; HRMS (EI) m/z calcd for $C_{15}H_{23}NO_5$ $[M]^+$ 297.1576, found 297.1580.

4-((*S*)-1-(Benzyloxy)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-propyl)-3-((benzyloxy)methyl)-2-methoxypyridine (12). Sodium hydride (1.1 g, 27 mmol) was added in two portions to a solution of compound **11** (2.0 g, 6.73 mmol) in 40 mL of anhydrous THF at room temperature under nitrogen, the mixture was stirred for 30 min at the same temperature, and then benzyl bromide (3.0 mL, 27 mmol) was added. The mixture was heated for 4 h at 70 °C, cooled to room temperature, and poured into 20 mL water. The solution was extracted with EA, washed with brine, dried over anhydrous Na_2SO_4, and concentrated to afford crude **12**, which was further purified by column chromatography (ethyl acetate/hexane =1:5) to give pure **12** as a colorless liquid (2.8 g, 88% yield). The crude product could be used in the next step without further purification when in a large scale: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, J = 7.25 Hz, 3H), 1.35 (s, 6H), 2.20 (m, 1H), 2.30 (m, 1H), 3.85 (m, 1H), 3.97(s, 3H), 4.00 (m, 1H), 4.45 (s, 2H), 4.47 (d, J = 9.6 Hz, 1H), 4.68 (m, 2H), 4.79 (t, 1H), 4.87 (d, J = 9.6 Hz, 1H), 7.11 (d, J = 5.6 Hz, 1H), 7.25−7.36 (m, 10H), 8.10 (d, J = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.6, 14.1, 20.8, 24.5, 25.9, 26.6, 53.6, 60.2, 63.9, 65.4, 65.6, 73.2, 80.4, 82.2, 109.5, 116.4, 119.2, 127.1, 127.3, 128.1, 138.4, 138.9, 146.0, 151.1, 164.3; MS (EI) m/z = 477; HRMS (EI) m/z calcd for $C_{29}H_{35}NO_5$ $[M]^+$ 477.2515, found 477.2508.

(2*R*,3*S*)-3-(Benzyloxy)-3-(3-((benzyloxy)methyl)-2-methoxypyridin-4-yl)pentane-1,2-diol (13). To a solution of compound **12** (2.5 g, 5.23 mmol) in methanol (30 mL) was added concentrated HCl (6 mL) at room temperature and the mixture stirred for another 2 h. Then the mixture was poured into water (100 mL). The solution was extracted with CH_2Cl_2, washed with brine, dried over anhydrous Na_2SO_4, and evaporated to dryness to give a viscous solid **13** (2.1 g, 92.1% yield), which was pure enough to use in the next step without further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, J = 7.0 Hz, 3H), 2.16 (m, 1H), 2.30 (s, 1H), 2.45 (m, 1H), 3.31 (m, 1H), 3.54 (m, 1H), 3.93 (s, 3H), 3.99 (s, 1H), 4.11 (m, 1H), 4.35 (d, J = 11.5 Hz, 1H), 4.44 (d, J = 11.5 Hz, 1H), 4.53 (d, J = 10.5 Hz, 1H), 4.67 (d, J = 9.5 Hz, 1H), 4.74 (d, J = 10.5 Hz, 1H), 4.96 (d, J = 9.5 Hz, 1H), 6.88 (d, J = 5.5 Hz, 1H), 7.26−7.42 (m, 10H), 8.09 (d, J = 5.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.9, 25.1, 53.7, 63.3, 63.8, 64.9, 72.8, 77.3, 85.0, 116.4, 119.0, 127.4, 127.6, 127.9, 128.3, 137.7, 138.2, 145.7, 151.1, 164.2; MS (ESI) m/z = 438.2 $[M + 1]^+$; FTMS m/z calcd for $C_{26}H_{32}NO_5$ $[M + 1]^+$ 438.2274, found 438.2275.

(*S*)-2-(Benzyloxy)-2-(3-((benzyloxy)methyl)-2-methoxypyridin-4-yl)butanal (14). Sodium periodate (1.2 g, 5.2 mmol) was added to a solution of compound **13** (1.16 g, 2.65 mmol) in 15 mL of acetonitrile and 2 mL of water, and then the mixture was stirred for 2 h

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at room temperature and poured into 20 mL water. The solution was extracted with CH_2Cl_2, washed with brine, dried over anhydrous Na_2SO_4, and evaporated to dryness to give a viscous solid **14** (1.02 g, 95% yield), which was used without further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, J = 7.0 Hz, 3H), 2.46 (m, 2H), 3.96 (s, 3H), 4.26 (d, J = 11.1 Hz, 1H), 4.33 (d, J = 11.1 Hz, 1H), 4.44 (s, 2H), 4.53 (d, J = 11.1 Hz, 1H), 4.59 (d, J = 11.1 Hz, 1H), 7.11 (d, J = 5.5 Hz, 1H), 7.23−7.35 (m, 10H), 8.16 (d, J = 5.5 Hz, 1H), 9.67 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.0, 25.2, 53.7, 65.1, 72.7, 85.5, 116.0, 118.4, 127.1, 127.5, 127.9, 128.0, 137.4, 146.6, 148.0, 163.7, 199.2; MS (EI) m/z = 405 $[M]^+$; HRMS (EI) m/z calcd for $C_{25}H_{27}NO_4$ $[M]^+$ 405.1940, found 405.1944.

(*S*)-2-(Benzyloxy)-2-(3-((benzyloxy)methyl)-2-methoxypyridin-4-yl)butanoic Acid (15). Compound **14** (1.1 g, 2.72 mmol) was added to a solution of 2-methyl-2-butylene (3 mL) and sodium dihydrogen phosphate (1.7 g) in 15 mL of acetonitrile and 5 mL of water. The mixture was stirred for 30 min, and sodium chlorite (1.0 g, 11 mmol) was added at room temperature. Then the mixture was stirred for 2 h and poured into 15 mL of 1 N HCl solution. The solution was extracted with CH_2Cl_2, washed with brine, dried over anhydrous Na_2SO_4, and evaporated to dryness give viscous liquid **15** (1.1 g, 96.0% yield), which was pure enough to use in the next step without further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, J = 7.0 Hz, 3H), 2.46 (m, 2H), 3.93(s, 3H), 4.30 (m, 3H), 4.45 (d, J = 10.0 Hz, 1H), 4.70 (d, J = 10.5 Hz, 1H), 4.88 (d, J = 10.0 Hz, 1H), 6.99 (d, J = 6.0 Hz, 1H), 7.19−7.37 (m, 10H), 8.15 (d, J = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.1, 26.1, 54.0, 62.9, 66.3, 72.8, 84.9, 115.7, 118.8, 127.5, 127.8, 127.9, 128.0, 128.1, 128.2, 128.4, 137.0, 137.6, 146.5, 148.8, 163.9, 173.5; TOF MS (EI) m/z = 421.1904 $[M]^+$; HRMS m/z calcd for $C_{25}H_{27}NO_5$ $[M]^+$ 421.1889, found 421.1896.

(*S*)-4-Ethyl-4-hydroxy-8-methoxy-1*H*-pyrano[3,4-*c*]pyridin-3(4*H*)-one (16). A mixture of compound **15** (1.0 g, 2.37 mmol) and methanol (30 mL) was hydrogenated at normal pressure and at room temperature for 12 h with 0.1 g 10% Pd/C. The catalyst was then filtered off and the filtrate was evaporated to dryness to give crude compound **16**, which was further purified by column chromatography (ethyl acetate/hexane =1:5) to give pure **16** as a colorless liquid (0.51 g, 85% yield). The crude product could be used in the next step without purification when in large scale: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (t, J = 7.35 Hz, 3H), 1.79 (m, 2H), 3.66 (s, 1H), 3.99 (s, 3H), 5.26 (d, J = 15.6 Hz, 1H), 5.57 (d, J = 15.6 Hz, 1H), 7.15 (d, J = 5.25 Hz, 1H), 8.15 (d, J = 5.25 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.4, 31.6, 53.6, 65.5, 72. 8, 111.2, 113.0, 147.1, 148.1, 158.6, 174.0; MS (EI) m/z = 223 $[M]^+$; HRMS m/z calcd for $C_{11}H_{13}NO_4$ $[M]^+$ 223.0845, found 223.0843.

(*S*)-4-Ethyl-4-hydroxy-8-methoxy-1*H*-pyrano[3,4-*c*]pyridin-3(4*H*)-one (5). Compound **16** (16.7 g, 74.9 mmol) was dissolved in 3 N HCl (300 mL) and the solution was heated for 3 h at 100 °C. The mixture was then cooled to room temperature and evaporated to dryness to give crude compound **5**, which was purified by trituration with 20 mL anhydrous ethanol affording product **5** (11.72 g, 75% yield) as a white solid: $[\alpha]_D^{25}$ = 110.77 (*c*, 0.30, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.80 (t, J = 7.5 Hz, 3H), 1.75 (m, 2H), 5.22 (s, 2H), 6.25 (s, 1H), 6.35 (d, J = 7.0 Hz, 1H), 7.42 (d, J = 7.0 Hz, 1H), 11.8 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 7.6, 30.4, 65.1, 71.9, 102.1, 119.0, 134.7, 149.9, 158.9, 172.5; MS (EI) m/z = 209 $[M]^+$; HRMS m/z calcd for $C_{10}H_{11}NO_4$ $[M]^+$ 209.0688, found 209.0692. The enantiomeric excess of (*S*)-**5** was determined by HPLC as 100% [column, CHIRALPAK OD-H (4.6 mm ×250 mm), room temperature; eluent, hexane-EtOH (90:10); flow rate, 1.0 mL/min; detect, 300 nm; t_R of (*S*)-**5**, 24.660 min; t_R of (*R*)-**5** (enantiomer of (*S*)-**5**), 17.509 min].

Ethyl 3-((4-Methoxy-2-propionylphenyl)amino)-3-oxopropanoate (17b). To a solution of compound **17a**[37] (7.2 g, 40.17 mmol) in CH_2Cl_2 (60 mL) and Et_3N (17 mL) was added ethyl 3-chloro-3-oxopropanoate (12.2 g, 81.03 mmol) in 40 mL of CH_2Cl_2 dropwise over 30 min at 0 °C. The mixture was stirred for further 30 min and water (100 mL) was added at room temperature. The solution was extracted with CH_2Cl_2, washed with brine, dried over anhydrous Na_2SO_4, and evaporated to dryness give compound **17b** (9.5 g, 81% yield): ^{1}HNMR ($CDCl_3$): δ 11.72 (s, 1 H), 8.62 (d, J = 9 Hz, 1 H), 7.41 (d, J = 3 Hz, 1 H), 7.11 (dd, 1 H), 4.26 (dd, 2 H), 3.84 (s, 3 H), 3.49 (s, 2 H), 3.04 (dd, 2 H), 1.31 (dd, 3 H), 1.22 (dd, 3 H).

Ethyl 4-Ethyl-6-methoxy-2-oxo-1,2-dihydroquinoline-3-carboxylate (17c). To a solution of compound **17b** (9.5 g, 32.39 mmol) in MeOH (80 mL) was added NaOMe (5.2 g, 92.26 mmol) at 0 °C. The mixture was stirred for 1 h and 1 N HCl was added. The solid was collected, washed with PE/EA (10/1) and dried to give compound **17c** (7.5 g, 85% yield): ^{1}H NMR ($CDCl_3$) δ 12.03 (s, 1 H), 7.33 (d, J = 10 Hz, 1 H), 7.18 (d, J = 10 Hz, 1 H), 7.15 (dd, 1 H), 4.48 (dd, 2 H), 3.87 (s, 3 H), 2.85 (dd, 2 H), 1.44 (t, J = 5 Hz, 3 H), 1.35 (t, J = 5 Hz, 3 H).

Ethyl 2-Chloro-4-ethyl-6-methoxyquinoline-3-carboxylate (17d). The solution of compound **17c** (1 g, 3.63 mmol) and $POCl_3$ (10 mL) was refluxed 1−3 h. The mixture was quenched by crashed ice. The solid was collected and dried to give compound **17d** (0.7 g, 66% yield): ^{1}H NMR ($CDCl_3$) δ 7.91 (d, J = 9 Hz, 1 H), 7.38 (q, 1 H), 7.25 (d, J = 4 Hz, 1 H), 4.54 (q, 2 H), 3.98 (s, 3 H), 3.04 (q, 2 H), 1.49 (t, J = 7 Hz, 3 H), 1.38 (t, J = 7 Hz, 3 H).

(2-Chloro-4-ethyl-6-methoxyquinolin-3-yl)methanol (17e). To a solution of compound **17d** (2 g, 6.81 mmol) in THF (20 mL) was added Red-Al (3.5 M, 7.0 mL) at 0 °C. The mixture was stirred for 1 h and poured into 1 N HCl (50 mL). The solid was collected and dried to give compound **17e** (1.4 g, 82% yield): ^{1}H NMR ($CDCl_3$) δ 7.90 (d, J = 9 Hz, 1 H), 7.38 (dd, 1 H), 7.25 (d, J = 9 Hz, 1 H), 4.99 (s, 2 H), 3.96 (s, 3 H), 3.23 (q, 2 H), 2.15 (br, 1 H), 1.35 (t, J = 5 Hz, 3 H).

2-Bromo-3-(bromomethyl)-4-ethyl-6-methoxyquinoline (17). To a solution of compound **17e** (1 g, 3.97 mmol) in $CHCl_3$ (15 mL) was added PBr_3 (1 mL). The mixture was refluxed for 12 h and quenched by water and $NaHCO_3$. The solution was extracted with $CHCl_3$, washed with brine, dried over anhydrous Na_2SO_4, and evaporated to dryness give compound **17** (1 g, 70% yield): ^{1}H NMR ($CDCl_3$) δ 7.86 (d, J = 9 Hz, 1 H), 7.33 (q, 1 H), 7.17 (d, J = 3 Hz, 1 H), 4.77 (s, 2 H), 3.91 (s, 3 H), 3.15 (q, 2 H), 1.36 (t, J = 8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 158.4, 157.4, 150.9, 143.1, 130.8, 127.2, 126.7, 122.6, 102.6, 61.6, 55.6, 27.5, 22.5, 14.2; MS (EI) m/z = 356 $[M]^+$; HRMS m/z calcd for $C_{13}H_{13}Br_2NO$ $[M]^+$ 356.9364, found 356.8490.

(*S*)-7-((2-Bromo-4-ethyl-6-methoxyquinolin-3-yl)methyl)-4-ethyl-4-hydroxy-1*H*-pyrano[3,4-*c*]pyridine-3,8(4*H*,7*H*)-dione (18). K_2CO_3 (2.76 g, 0.02 mol) was added to a solution of compound **17** (3.59 g, 0.01 mol) and compound **5** (2.09 g, 0.01 mol) in DMF (50 mL) under nitrogen. Then the mixture was heated for 4 h at 50 °C, and poured into 200 mL of 1 N HCl solution, extracted with dichloromethane, dried with anhydrous Na_2SO_4, and evaporated to dryness to afford crude **18**, which was further purified by trituration with petroleum ether/ethyl acetate (15 mL) to give pure **18** as an off-white solid (4.38 g, 90% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (t, J = 6.5 Hz, 3H), 1.17 (t, J = 7.6 Hz, 3 H), 1.78 (m, 2 H), 3.09 (m, 2 H), 3.60 (s, 1 H), 3.96 (s, 3 H), 5.23 (d, J = 16.2 Hz, 1 H), 5.54 (m, 2 H), 5.67 (d, J = 16.2 Hz, 1 H), 6.45 (d, J = 7.2 Hz, 1 H), 7.14 (d, J = 7.2 Hz, 1 H), 7.23 (d, J = 2.3 Hz, 1 H), 7.44 (dd, J = 2.3, 9.2 Hz, 1 H), 7.96 (d, J = 9.2 Hz, 1 H).

(*S*)-4,11-Diethyl-4-hydroxy-9-methoxy-1*H*-pyrano[3′,4′:6,7]-indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione (19). A mixture of bromoquinoline **18** (4.87 g, 0.01 mol), palladium(II) acetate (0.22 g, 1.0 mmol), anhydrous K_2CO_3 powder (3.46 g, 0.025 mol), and triphenylphosphine (1.05 g, 4.0 mmol) in 150 mL of toluene was brought to reflux under nitrogen. As the reflux was continued for 16 h, the product precipitated. Then the mixture was cooled to room temperature, and the precipitate was collected, washed with water and ethyl acetate, and dried to afford a pale yellow solid (2.85 g, 70% yield), which was used without further purification: ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.88 (t, J = 7.1 Hz, 3H), 1.33 (t, J = 7.5 Hz, 3H), 1.86 (m, 2H), 3.20 (q, J = 7.5 Hz, 2H), 3.99 (s, 3H), 5.30 (s, 2H), 5.42 (s, 2H), 6.52 (s, 1H), 7.27 (s, 1H), 7.52 (m, 2H), 8.08 (d, J = 9.0 Hz, 1H).

7-Ethyl-10-hydroxycamptothecin (SN-38, 4). A mixture of compound **19** (1.5 g, 3.69 mmol) and HBr solution (150 mL) was

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refluxed for 2 h. The mixture was cooled to room temperature and extracted with $CHCl_3$, dried with anhydrous Na_2SO_4, and evaporated to dryness to afford crude **4**, which was further purified by trituration with $CHCl_3$/MeOH to give pure **4** as an off-white solid (1.45 g, 87% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.88 (t, J = 7.25 Hz, 3H), 1.32 (t, J = 7.5 Hz, 3H), 1.87 (m, 2H), 3.10 (q, J = 7.5 Hz, 2H), 5.28 (s, 2H), 5.42 (s, 2H), 6.48(s, 1H), 7.25 (s, 1H), 7.41 (d, J = 10.0 Hz, 2H), 8.03 (d, J = 10.0 Hz, 1H), 10.3 (s, 1H); The enantiomeric excess of (*S*)-SN-38 was determined by HPLC as 100% [column, CHIRALPAK AD-H (4.6 mm × 250 mm), room temperature; eluent, EtOH; flow rate, 0.4 mL/min; detect, 220 nm; t_R of (*S*)-SN-38, 10.665 min; t_R of (*R*)-**SN-38** (enantiomer of (*S*)-**SN-38**), 14.906 min].

Camptothecin (1): yield 53% (two steps from **5** and 2-bromo-3-(bromomethyl)quinoline); $[\alpha]_D^{25}$ = 42.85 (*c*, 0.40, MeOH/$CHCl_3$);[13] ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.89 (t, J = 7.3 Hz, 3H), 1.88 (m, 2H), 5.27 (s, 2H), 5.43 (s, 2H), 6.52 (s, 1H), 7.35 (s, 1H), 7.71 (t, J = 7.2 Hz, 1H), 7.86 (t, J = 8.0 Hz, 1H), 8.11 (d, J = 8.1 Hz, 1H), 8.16 (d, J = 8.4 Hz, 1H), 8.68 (s, 1H); MS (ESI): m/z = 349.2 $[M + 1]^+$; HRMS m/z calcd for $C_{20}H_{17}N_2O_4[M + 1]^+$ 349.11828, found 349.11877. The enantiomeric excess of (*S*)-**1** was determined by HPLC as 99.9258% [column, CHIRALPAK OJ-H (4.6 mm × 250 mm), room temperature; eluent, EtOH; flow rate, 0.4 mL/min; detect, 254 nm; t_R of (*S*)-**1**, 18.835 min; t_R of (*R*)-**1** (enantiomer of (*S*)-**1**), 15.524 min]. ee = 99.9258%.

10-Hydroxycamptothecin: yield 34.7% (three steps from **5** and 2-bromo-3-(bromomethyl)-6-methoxyquinoline); ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.88 (t, J = 7.25 Hz, 3H), 1.86 (m, 2H), 5.23 (s, 2H), 5.41 (s, 2H), 6.50 (s, 1H), 7.27(d, J = 8.0 Hz, 2H), 7.42 (d, J = 8.0 Hz, 1H), 8.02 (d, J = 8.0 Hz, 1H), 8.45 (s, 1H), 10.3 (s, 1H). The enantiomeric excess of (*S*)-**10-HCPT** was determined by HPLC as 99.92% [column, CHIRALPAK OJ-Hs (4.6 mm × 250 mm), room temperature; eluent, MeOH; flow rate, 0.6 mL/min; detect, 220 nm; t_R of (*S*)-**10-HCPT**, 10.384 min; t_R of (*R*)-**10-HCPT** (enantiomer of **10-HCPT**), 8.378 min]. ee = 99.92%.

■ ASSOCIATED CONTENT

Supporting Information

Copy of X-ray structure of the key intermediate **10**, copies of ^{1}H and ^{13}C NMR spectra of **10**−**16**, copies of ^{1}H NMR spectra of **19**, **4**, **1** and **10-OH-CPT**, and copies of HPLC of **4**, **1** and **10-OH-CPT**. Copies of ^{1}H and ^{13}C NMR spectra of compound **17**. Crystallographic data for **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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