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ORIGINAL PAPER

Synthesis of the DE synthon of racemic camptothecin

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Abstract A concise formal synthesis of camptothecin is described. The key pyrido-lactone (DE ring) was prepared effectively starting from 2-chloronicotinic acid via lithiation, reduction, and hydrolysis in 29% overall yield.

Keywords Pyridone · Lactone · 2-Chloronicotinic acid · Lithiation · Camptothecin

Introduction

Camptothecin (CPT, **1**), a natural alkaloid, was first isolated from *Camptotheca acuminata* (*Xi Shu*) by Wani and Wall in 1966 [1]. The primary cellular target of the family of camptothecin products, with camptothecin as lead, is the covalent binary complex formed between DNA and topoisomerase I (Topo I) during DNA relaxation, and stabilization of this complex by camptothecin was believed to lead to cell death [2, 3]. Thus, CPT and its analogues showed potent antitumor activity. Two camptothecin analogues, topotecan (**2**) [4] and irinotecan (**3**) [5, 6], have been approved by the Food and Drug Administration (FDA) to treat cancers. While one of its analogues, foetidine (**4**), exhibits anti-human immunodeficiency virus (HIV) activity [7], other analogues are in different stages of clinical and preclinical trials [8] (Scheme 1).

Due to its excellent biological activity, unique mode of action, and challenging pentacyclic structure, camptothecin has been a popular compound over four decades for study by both medicinal and synthetic chemists. In 1971, Stork and Schultz [9] first reported the total synthesis of camptothecin, which as one of the key steps involves annulation of an ester carbonate and unsaturated lactone. Subsequently, Corey [10] first reported the asymmetric total synthesis of camptothecin in 1975. To date, methods of synthesis of CPT and its analogues have been reported by many innovative approaches using different processes as the key step [11–42], such as cascade radical cyclization [43], Friedlander condensation [44], Michael addition [45, 46], and the Diels–Alder reaction [47, 48]. However, synthesis of camptothecin still remains a challenge, since most of the known synthetic routes are lengthy, of low overall efficiency, and of high cost. As part of our research program, we have directed our efforts towards a more practical and efficient strategy to build the camptothecin structure using simple starting materials and reactions.

Results and discussion

After having reviewed the reported methods for synthesis of camptothecin and its analogues, we decided to use the classical Comins' approach (Scheme 2), wherein the C ring is created by condensation of 2-bromo-3-(bromomethyl)quinoline (AB ring) with pyridone derivative **5** (DE ring). Thus, the construction of the DE ring is the pivotal and difficult point [49]. Herein we report a novel approach for construction of the DE synthon of camptothecin.

Structure analysis shows that the pyridone **5** possesses three substituent groups at C2, C3, and C4-positions. 2-Chloronicotinic acid is a very cheap commercial chemical; its carboxylic group could be reduced to a hydroxymethyl group and the 2-chloro group could be converted to a 2-keto group by hydrolysis. According to the literature

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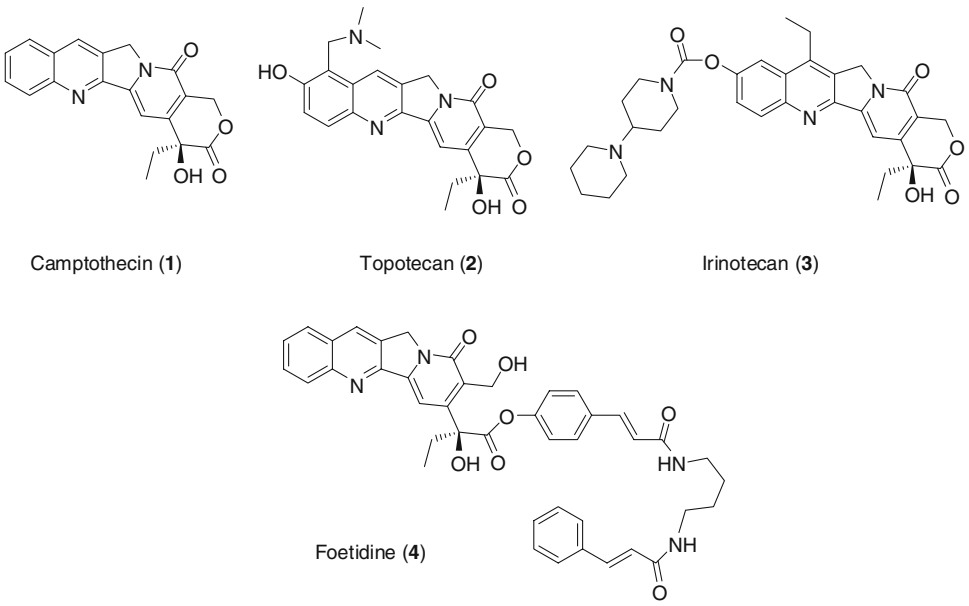
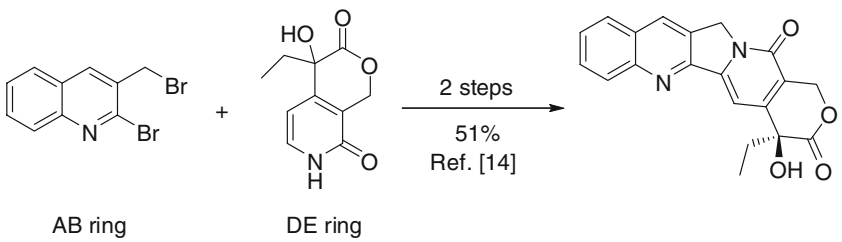
Scheme 1



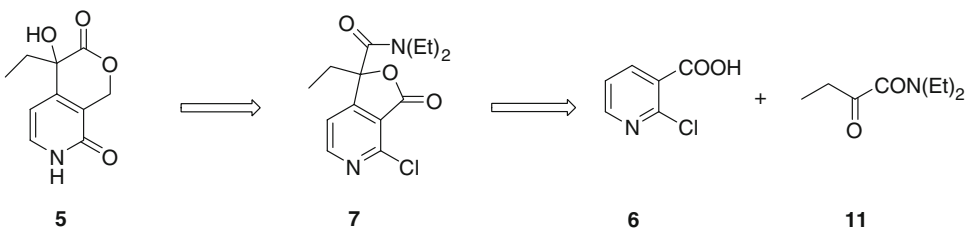
Scheme 2



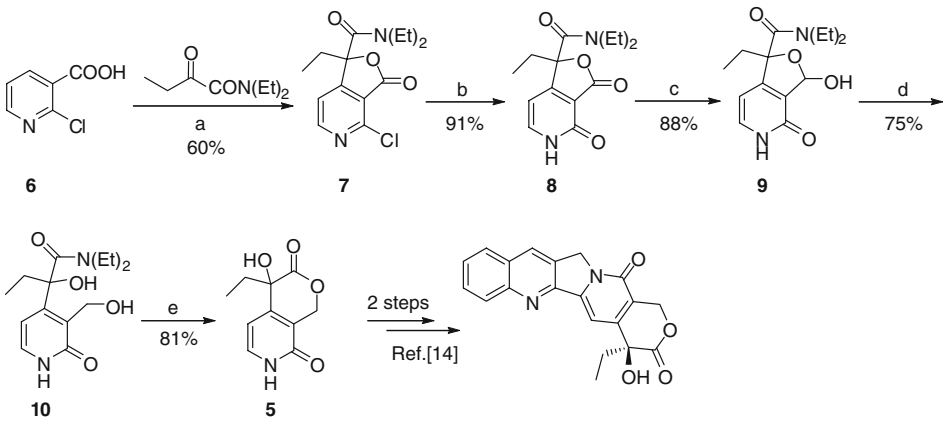
[50, 51], many polyfunctional pyridines could be constructed via lithiation and subsequent electrophilic additions [52–55]. Moreover, the lithiation of pyridinecarboxylic acids occurs at the position *ortho* to the carboxyl group [56, 57], which makes the introduction of functional groups at the C4-position very effective. Based on these considerations, 2-chloronicotinic acid (**6**) and *N*,*N*-diethyl-2-oxobutyramide (**11**) were selected for the construction of the DE ring via our strategy, which is highlighted retrosynthetically in Scheme 3.

As is shown in Scheme 4, 2-chloronicotinic acid (**6**) was deprotonated with 3 equiv lithium 2,2,6,6-tetramethylpiperidine (LTMP) and 1 equiv *n*-BuLi in anhydrous THF at −78 °C under nitrogen. The intermediate dilithio derivative reacted with *N*,*N*-diethyl-2-oxobutyramide (**11**) and provided lactone **7** in 60% yield. The resulting lactone **7** was then refluxed in AcOH to produce pyridone **8** in excellent yield (91%). It should be noted that synthesis of pyridone **8** has been reported by Peters and co-workers [25] through a five-step strategy in a yield of 24%. Thus, our two-step synthesis with 55% overall yield is much more efficient and appealing. However, the direct reduction of pyridone **8** into diol **10** with different hydride-reducing compounds ($NaBH_4$, $LiBH_4$, or $LiAlH_4$) resulted in low yields. Thus, a two-step reduction was attempted. Treatment of pyridone **8** with sodium borohydride and cerium(III) chloride heptahydrate in absolute ethanol afforded lactol **9** in 88% yield. Subsequently, reduction of lactol **9** into **10** with aluminum isopropoxide was executed in good yield. Finally, the desired diol **10** was hydrolyzed

Scheme 3



Scheme 4



Reagents and conditions: (a) *n*-BuLi (4 equiv), TMP (3 equiv), -78°C. (b) AcOH, reflux, 6 h. (c) $NaBH_4$ (10 equiv), $CeCl_3.7H_2O$ (2.5 equiv), ethanol, 30 min. (d) $(i\text{-PrO})_3Al$ (2 equiv). (e) 1N HCl, reflux, 3h.

to give pyridone **5** in 82% yield. Finally, the camptothecin and 10-hydroxycamptothecin targets were obtained from the pyrido-lactone **5** via Comins' approach [49].

In summary, the total synthesis of racemic camptothecin was developed by using the pyrido-lactone **5** as a pivotal substrate. The latter was obtained in five steps from 2-chloronicotinic acid (**6**) using lithiation as the key step, in 29% overall yield. This approach offers a practical synthetic route for racemic camptothecin and its analogues. Finally, on the basis of this approach, the total asymmetric synthesis of camptothecin is currently in progress in our group.

Experimental

^{1}H nuclear magnetic resonance (NMR) spectra were recorded on a Bruker DRX-500 (500 MHz). ^{13}C NMR spectra were obtained on a JNM-EX400 (100 MHz). Mass spectra (MS) were determined on a Finnigan MAT-95 mass spectrometer.

4-Chloro-N,N,1-triethyl-1,3-dihydro-3-oxofuro[3,4-c]pyridine-1-carboxamide (**7**, $C_{14}H_{17}ClN_2O_3$)

n-BuLi (58.5 cm^3, 2.5 M in *n*-hexane) was added to a solution of 14.4 cm^3 2,2,6,6-tetramethylpiperidine (117.6 mmol) in 200 cm^3 anhydrous THF at −78 °C under nitrogen. The mixture was stirred for 30 min at the same temperature, before 5.0 g 2-chloronicotinic acid (31.64 mmol) was added. After 30 min at −78 °C, 17.2 g *N*,*N*-diethyl-2-oxobutyramide (109.5 mmol) was added and stirred for another 30 min. Then the mixture was allowed to reach room temperature and hydrolyzed with 50 cm^3 1 N HCl. The mixture was extracted with ethyl acetate, dried over anhydrous Na_2SO_4, and concentrated to afford 25.0 g crude **7**, which was further purified by column chromatography (ethyl acetate:hexane = 1:5) to give pure **7** as a white solid (5.66 g, 60% yield). M.p.: 53 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.84$ (t, $J = 7.0$ Hz, 3H), 1.15 (t, $J = 7.0$ Hz, 3H), 1.26 (t, $J = 7.0$ Hz, 3H), 2.15 (m, 1H), 2.40 (m, 1H), 3.14 (m, 1H), 3.28 (m, 1H), 3.51 (m, 1H), 3.98 (m, 1H), 7.86 (d, $J = 5.0$ Hz, 1H), 8.63 (d, $J = 5.0$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 7.51$, 12.27, 14.59, 32.57, 42.58, 89.09, 119.95, 148.97, 153.19, 161.81, 164.86, 165.98, 189.04 ppm; MS (EI): $m/z = 296$; HRMS (EI): m/z calcd for $C_{14}H_{17}N_2O_3$ $[M]^+$ 296.0928, found 296.0926.

N,N,1-Triethyl-1,3,4,5-tetrahydro-3,4-dioxofuro[3,4-c]pyridine-1-carboxamide (**8**, $C_{14}H_{18}N_2O_4$)

Compound **7** (1.5 g, 5.03 mmol) was dissolved in 40 cm^3 acetic acid, and the solution was heated for 6 h at 120 °C. The mixture was then cooled to room temperature and poured into 80 cm^3 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 white solid (1.27 g, 91%), which was used without further purification. M.p.: 176 °C (Ref. [25] m.p.: 177 °C); ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 0.88$ (t, $J = 7.5$ Hz, 3H), 1.14 (t, $J = 7.0$ Hz, 3H), 1.24 (t, $J = 6.5$ Hz, 3H), 2.09 (m, 1H), 2.38 (m, 1H), 3.15 (m, 1H), 3.26 (m, 1H), 3.50 (m, 1H), 3.94 (m, 1H), 6.93 (d, $J = 6.5$ Hz, 1H), 7.80 (d, $J = 6.5$ Hz, 1H), 13.17 (bs, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 12.25$, 14.38, 30.62, 41.90, 87.75, 101.76, 111.09, 143.17, 157.12, 165.56, 166.04, 168.42 ppm; MS (EI): $m/z = 278$; HRMS (EI): m/z calcd for $C_{14}H_{18}N_2O_4$ $[M]^+$ 278.1267, found 278.1266.

2-(1,2-Dihydro-3-hydroxymethyl-2-oxopyridin-4-yl)-N,N-diethyl-2-hydroxybutyramide (**10**, $C_{14}H_{22}N_2O_4$)

$NaBH_4$ (1.09 g, 28.8 mmol) was added in two portions to a cold (0 °C) solution of 0.8 g compound **8** (2.88 mmol) and 2.68 g cerium(III) chloride heptahydrate (7.2 mmol) in anhydrous ethanol (80 cm^3) over 30 min. After warming to

room temperature, the mixture was poured into 200 cm^3 saturated $NaHCO_3$/NaCl solution (1:1) and extracted with 250 cm^3 EtOH/CH_2Cl_2 (1:4). The combined extracts were dried over anhydrous Na_2SO_4 and evaporated to dryness to give **9** as a white solid (0.88 g, 88%). A mixture of 0.6 g crude compound **9** (2.14 mmol) and 0.87 g aluminum isopropoxide (4.28 mmol) in 40 cm^3 isopropanol was refluxed for 2 h at 85 °C. The mixture was then cooled to room temperature and quenched with 20 cm^3 1 N HCl. The solution was then extracted with 200 cm^3 EtOH/CH_2Cl_2 (1:4), dried over anhydrous Na_2SO_4, and evaporated to dryness to give an off-white solid, which was purified by trituration with 5 cm^3 CH_2Cl_2, affording product **10** (0.45 g, 75%) as a white solid. M.p.: 196 °C (Ref. [25] m.p.: 193 °C); ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 0.69$ (t, $J = 7.1$ Hz, 3H), 0.75 (t, $J = 6.2$ Hz, 3H), 1.01 (t, $J = 6.9$ Hz, 3H), 1.87 (m, 1H), 2.07 (m, 1H), 3.11 (m, 1H), 3.32 (m, 1H), 4.39 (s, 1H), 4.66 (s, 1H), 6.40 (d, $J = 7.0$ Hz, 1H), 7.30 (d, $J = 7.0$ Hz, 1H), 11.62 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 12.22$, 12.58, 32.76, 55.64, 77.91, 103.78, 126.76, 132.35, 152.55, 163.27, 171.54, 168.42 ppm; MS (EI): $m/z = 282$; HRMS (EI): m/z calcd for $C_{14}H_{22}N_2O_4$ $[M]^+$ 282.1580, found 282.1582.

4-Ethyl-4-hydroxy-1H-pyrano[3,4-c]pyridine-3,8(4H,7H)-dione (**5**, $C_{10}H_{11}NO_4$)

A solution of 0.266 g compound **10** (0.943 mmol) in 12 cm^3 3 N HCl was heated for 1 h at 100 °C. The mixture was cooled to room temperature and evaporated to dryness to give a straw-yellow solid. Purification of the latter with anhydrous ethanol yielded product **9** (0.16 g, 81%) as a white solid. M.p.: 226 °C (Ref. [25] m.p.: 227 °C); ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 0.80$ (t, $J = 7.0$ Hz, 3H), 1.74 (m, 2H), 5.22 (s, 2H), 6.23 (s, 1H), 6.35 (d, J = 7.0 Hz, 1H), 7.42 (d, J = 7.0 Hz, 1H), 11.82 (bs, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 30.35$, 65.10, 71.88, 102.07, 119.00, 134.66, 149.86, 158.85, 172.52 ppm; MS (EI): $m/z = 209$; HRMS (EI): m/z calcd for $C_{10}H_{11}NO_4$ $[M]^+$ 209.0688, found 209.0692.

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References

1. Wall ME, Wani MC, Cook CE, Palmer KH, McPhail AT, Sim GA (1966) J Am Chem Soc 88:3888
2. Hsiang YH, Hertzberg R, Hecht S, Liu LF (1985) J Biol Chem 260:14873
3. Holm C, Covey JM, Kerrigan D, Pommier Y (1989) Cancer Res 49:6365
4. Kingsbury WD, Boehm JC, Jakas DR, Holden KG, Hecht SM, Gallagher G, Caranfa MJ, McCabe FL, Faucette LF, Johnson RK, Hertzberg RP (1991) J Med Chem 34:98
5. Negoro S, Fukuoka M, Masuda N, Takada M, Kusunoki Y, Matsui K, Takifuji N, Kudoh S, Niitani H, Taguchi TJ (1991) J Natl Cancer Inst 83:1164
6. Kawato Y, Aonuma M, Hirota Y, Kuga H, Sato K (1991) Cancer Res 51:4187
7. Priel E, Showalter SD, Blair DG (1991) AIDS Res Hum Retroviruses 7:65
8. Cragg GM, Newman DJ (2004) J Nat Prod 67:232
9. Stork G, Schultz AG (1971) J Am Chem Soc 93:4074
10. Corey EJ, Crouse DN, Anderson JE (1975) J Org Chem 40:2140
11. Plattner JJ, Gless RD, Cooper GK, Rapoport H (1974) J Org Chem 39:303
12. Wani MC, Ronman PE, Lindley JT, Wall ME (1980) J Med Chem 23:554
13. Hutchinson CR (1981) Tetrahedron 37:1047
14. Ciufolini MA, Roschangar F (1997) Tetrahedron 53:11049
15. Wall ME, Wani MC (1998) Alkaloids 50:509
16. Tagami K, Nakazawa N, Sano S, Nagao Y (2000) Heterocycles 53:771
17. Comins DL, Nolan JM (2001) Org Lett 3:4255
18. Du W (2003) Tetrahedron 59:8649
19. Yu J, Depue J, Kronenthal D (2004) Tetrahedron Lett 45:7247
20. Twin H, Batey RA (2004) Org Lett 6:4913
21. Thomas OP, Dumas C, Zaparucha A, Husson HP (2004) Eur J Org Chem 5:1128
22. Anderson RJ, Raolji GB, Kanazawa A, Greene AE (2005) Org Lett 7:2989
23. Brunin T, Hénichart JP, Rigo B (2005) Tetrahedron 61:7916
24. Rahier NJ, Cheng K, Gao R, Eisenhauer BM, Hecht SM (2005) Org Lett 7:835
25. Peters R, Althaus M, Nagy AL (2006) Org Biomol Chem 4:498
26. Li QY, Zu YG, Shi RZ, Yao LP (2006) Curr Med Chem 13:2021
27. Elban MA, Sun W, Eisenhauer BM, Gao R, Hecht SM (2006) Org Lett 8:3513
28. Dai W, Petersen JL, Wang KK (2006) Org Lett 8:4665
29. Xiao X, Antony S, Pommier Y, Cushman M (2006) J Med Chem 49:1408
30. Hiroya K, Kawamoto K, Sakamoto T (2006) Synlett 2636
31. Tang CJ, Babjak M, Anderson RJ, Greene AE, Kanazawa A (2006) Org Biomol Chem 4:3757
32. Chavan SP, Pathak AB, Kalkote UR (2007) Tetrahedron Lett 48:6561
33. Zhou HB, Liu GS, Yao ZJ (2007) Org Lett 9:2003
34. Zhou HB, Liu GS, Yao ZJ (2007) J Org Chem 72:6270
35. Liu GS, Dong QL, Yao YS, Yao ZJ (2008) Org Lett 10:5393
36. Chavan SP, Dhawane AN, Kalkote UR (2008) Synlett 2781
37. Cheng KJ, Rahier NJ, Eisenhauer BM, Gao R, Thomas SJ, Hecht SM (2005) J Am Chem Soc 127:838
38. Brunin T, Legentil L, Hénichart J-P, Rigo B (2006) Tetrahedron 62:3959
39. Cinelli MA, Morrell A, Dexheimer TS, Scher ES, Pommier Y, Cushman M (2008) J Med Chem 51:4609
40. Zhang LP, Bao Y, Kuang YY, Chen FE (2008) Helv Chim Acta 91:2057
41. Pin F, Comesse S, Sanselme M, Daïch A (2008) J Org Chem 73:1975
42. Boisse T, Gavara L, Hénichart J-P, Rigo B, Gautret P (2009) Tetrahedron 65:2455
43. Curran DP, Liu H (1991) J Am Chem Soc 113:2127
44. Wall ME, Wani MC, Natschke SM, Nicholas AW (1986) J Med Chem 29:1553
45. Ciufolini MA, Roschangar F (1990) Angew Chem Int Ed 35:1692
46. Chavan SP, Venkatraman MS (1998) Tetrahedron Lett 39:6745

47. Fortunak JMD, Mastrocola AR, Mellinger M, Sisti NJ, Wood JL, Zhuang ZP (1996) Tetrahedron Lett 37:5679
48. Boger DL, Hong J (1998) J Am Chem Soc 120:1218
49. Comins DL, Hang H, Saha JK, Jianhua G (1994) J Org Chem 59:5120
50. Lazaar J, Hoarau C, Mongin F, Trécourt F, Godard A, Quéguiner G, Marsais F (2005) Tetrahedron Lett 46:3811
51. Mongin F, Trécourt F, Quéguiner G (1999) Tetrahedron Lett 40:5483
52. Godard A, Marsais F, Plé N, Trécourt F, Turck A, Quéguiner G (1995) Heterocycles 40:1055
53. Quéguiner G, Marsais F, Snieckus V, Epsztajn J (1991) Adv Heterocycl Chem 52:187
54. Trécourt F, Gervais B, Mongin O, Le Gal C, Mongin F, Quéguiner G (1998) J Org Chem 63:2892
55. Pasquinet E, Rocca P, Marsais F, Godard A, Quéguiner G (1998) Tetrahedron 54:8771
56. Mortier J, Moyroud J, Bennetau B, Cain PA (1994) J Org Chem 59:4042
57. Bennetau B, Mortier J, Moyroud J, Guesnet JL (1995) J Chem Soc Perkin Trans 1 1265