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A practical formal synthesis of camptothecin

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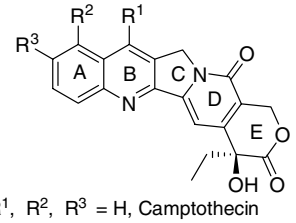
Abstract—The synthesis of the DE ring of camptothecin using simple and inexpensive starting materials, employing an addition elimination reaction and selective esterification of an aliphatic carboxylic acid as key steps is described.

Camptothecin **1** was isolated from the Chinese plant *Camptotheca acuminata* by Wall and Wani in 1966.[1] Camptothecin and its analogues collectively called camptothecins, have been isolated from various plant species,[2] and show potent antitumour activity and a unique mechanism of action, which inhibits DNA topoisomerase I. Camptothecin cannot be used as a drug due to its low solubility and toxic nature but its two analogues, irinotecan **2** and topotecan **3** are marketed as anticancer drugs and others are in clinical trials.



1 R^1, R^2, R^3 = H, Camptothecin

2 R^1 = Et, R^2 = H, R^3 = OCON–N, .HCl $3H_2O$, Irinotecan

3 R^1 = H, R^2 = CH_2NMe_2.HCl, R^3 = OH, Topotecan

The main structural feature of camptothecin is, a pentacyclic quinoline alkaloid containing an unstable six-membered α-hydroxy lactone. Camptothecin and its analogues show significant biological activity against various cancers and recently one of its analogues Foetidine has been shown to exhibit potent anti-HIV activity.[3]

Due to its challenging structure and broad spectrum of activity **1** has attracted significant attention from synthetic and medicinal chemists and pharmacologists.

To date, a number of syntheses of **1** have been reported, the first total synthesis being described by Stork et al. in 1971.[4] However, due to its low availability and high demand, our group has been interested in developing a simple and practical synthesis of camptothecin and its derivatives. Various approaches have been developed by us,[5a–c] for the construction of the D ring of camptothecin. The clinical use of **1** has been limited by its insolubility and toxicity, but extensive structure activity relation studies have identified many analogues with better solubility and with equal or better antitumour activity. Synthetic approaches towards these analogues have typically involved syntheses of suitably functionalized CDE-rings or DE-rings or precursors thereof, which have then been coupled with suitable counterparts. Recently, Hiroya et al.[6] synthesized the DE ring of camptothecin employing a Lewis acid catalyzed Michael addition on pyridone, however, selective introduction of a nucleophile at the 4-position was a problem, which also furnished the product of nucleophilic addition at C-6 in low yields.

Here we report a simple and practical synthesis of the DE-ring of camptothecin from simple and inexpensive starting materials employing an addition elimination reaction on 4-chlorodihydropyridone as the key step Scheme 1.

The synthesis commenced from **4** as the starting material, which was prepared according to the literature procedure.[7] Ketoester **4** was refluxed with $POCl_3$ in anhydrous dichloromethane to deliver 4-chlorodihydropyridone **5** in

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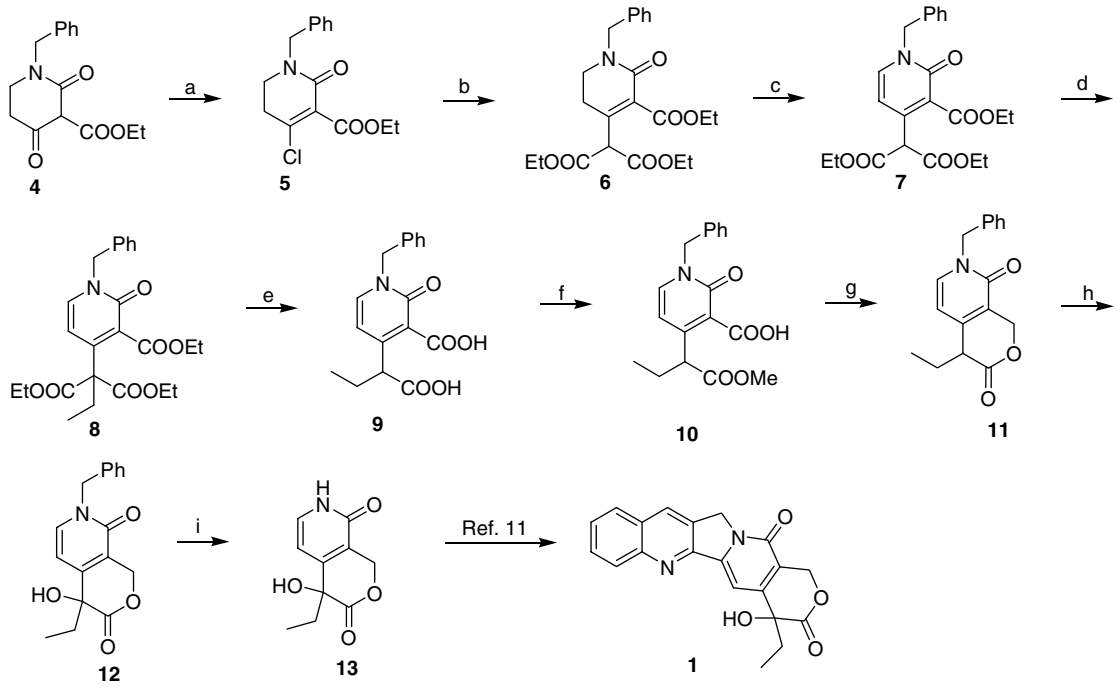

Scheme 1. Reagents and conditions: (a) $POCl_3$ (1.2 equiv), CH_2Cl_2, reflux, 3 h, 97%. (b) NaH (1.2 equiv), diethyl malonate (1.2 equiv), C_6H_6, rt, overnight, 85%. (c) DDQ (1.2 equiv), anhydrous 1,4 dioxane, reflux, 6 h, 96%. (d) K_2CO_3 (3.0 equiv), ethyl iodide (1.2 equiv), anhydrous acetone, reflux, 12 h, 91%. (e) LiOH (5.0 equiv), EtOH, rt, 24 h, 84%. (f) $NiCl_2$ (0.1 equiv), MeOH, reflux, 12 h, 76%. (g) (i) Et_3N (1.0 equiv), methyl chloroformate (1.0 equiv), anhydrous THF, 0 °C, 1 h. (ii) $NaBH_4$ (4.0 equiv), −78 °C, 3 h, 10% HCl, rt, 12 h, 84%. (h) $CuCl_2$ (4.0 equiv), Me_2NH, O_2, DMF, rt, 24 h, 92%. (i) $Pd(OH)_2$, H_2, EtOH, 50 °C, 5 h, 62%.

excellent yield. The addition–elimination reaction of diethyl malonate was accomplished on **5** using sodium hydride as a base to furnish product **6** in very good yield. Aromatization of dihydropyridone **6** was carried out using DDQ in refluxing 1,4-dioxane to furnish pyridone **7** in 96% yield. Alkylation of **7** with ethyl iodide gave alkylated product **8** in 91% yield. Ester hydrolysis followed by decarboxylation was achieved in one-pot using excess lithium hydroxide at room temperature to furnish diacid **9**. The selective mono esterification of the non-aromatic acid in the presence of the aromatic acid was accomplished using nickel chloride as the catalyst to deliver compound **10** in good yield.[8] Aromatic acid **10** was subjected to treatment with methyl chloroformate using triethylamine as base in THF at 0 °C to form a mixed anhydride and subsequent reduction of the mixed anhydride to the alcohol followed by lactonization was achieved using $NaBH_4$ to furnish **11** in 84% yield.[9] It is pertinent to mention that compared to our earlier synthesis[5a] for selective differentiation of an ester, here we avoided the use of DIBAL-H, which is hazardous, difficult to handle and involves a tedious workup. Hydroxylation of **11** was carried out using $CuCl_2$ and a catalytic amount of dimethylamine under an oxygen atmosphere to afford α-hydroxy lactone **12** in 98% yield.[10] Finally N-debenzylation of **12** was successfully carried out employing a catalytic amount of palladium hydroxide in ethanol under H_2 at 50 °C to furnish the desired DE-ring synthon **13** in 62% yield. The spectral data of compound **13** was in complete agreement with reported data.[11] Since **13** was also an intermediate in Comins' synthesis of **1**,[12] this constitutes a formal synthesis of camptothecin.

In conclusion, we have achieved a practical formal synthesis of camptothecin **1** employing an addition elimination reaction and selective differentiation of an aliphatic carboxylic acid over a heteroaromatic carboxylic acid as the key steps in 22% overall yield. This strategy could also be useful for the synthesis of the CDE-ring of **1** synthon of camptothecin and its analogues.

Acknowledgement

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References and notes

1. Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; McPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1966**, *88*, 3888–3890.
2. (a) Hecht, S. M.; Newman, D. J.; Kingston, D. G. I. *J. Nat. Prod.* **2000**, *63*, 1273–1276; (b) Das, B.; Madhusudan, P.; Reddy, P. V.; Anita, Y. *Indian J. Chem.* **2001**, *40B*, 453; (c) Kitajima, M.; Yoshida, S.; Yamagata, K.; Nakamura, M.; Takayama, H.; Saito, K.; Seki, H.; Aimi, N. *Tetrahedron* **2002**, *58*, 9169; (d) Puri, S. C.; Verma, V.; Amna, T.; Quzi, G. N.; Spiteller, M. *J. Nat. Prod.* **2005**, *68*, 1717.
3. Priel, E.; Showalter, S. D.; Blair, D. G. *AIDS Res. Hum. Retroviruses* **1991**, *7*, 65–72.
4. Stork, G.; Schultz, A. G. *J. Am. Chem. Soc.* **1971**, *93*, 4074.
5. (a) Chavan, S. P.; Venkatraman, M. S. *Tetrahedron Lett.* **1998**, *39*, 6745–6748; (b) Chavan, S. P.; Sivappa, R.

Tetrahedron Lett. **2004**, *45*, 3113–3115; (c) Chavan, S. P.; Pasupathy, K.; Venkatraman, M. S.; Kale, R. R. *Tetrahedron Lett.* **2004**, *45*, 6879–6882.
6. Hiroya, K.; Kawamoto, K.; Sakamoto, T. *Synlett* **2006**, 2636–2640.
7. Ibenmoussa, S.; Chavignon, O.; Teulade, J.-C.; Viols, H.; Debouzy, J.-C.; Chapat, J.-P.; Gueiffier, A. *Heterocycl. Commun.* **1998**, *4*, 317–324.
8. Ram, R. N.; Charles, I. *Tetrahedron* **1997**, *53*, 7335–7340.
9. Su, J.; Qiu, G.; Liang, S.; Hu, X. *Synth. Commun.* **2005**, *35*, 1427.
10. Rapoport, H.; Tang, C. S. F.; Morrow, C. J. *J. Am. Chem. Soc.* **1975**, *97*, 159–167.
11. Spectral data of compound **13**: Mp: 225 °C (lit. 227 °C); IR ($CHCl_3$) *v*: 3273, 2930, 1754, 1651, 1620, 1472, 1470, 1160, 837 cm^{-1}; ^1H NMR ($CDCl_3$+CCl_4+DMSO-d_6, 400 MHz) δ: 0.98 (t, $J = 7.2$ Hz, 3H), 1.80 (q, $J = 7.2$ Hz, 2H), 3.72 (s, 1H), 5.15 (d, $J = 16.1$ Hz, 1H), 5.55 (d, $J = 16.1$ Hz, 1H), 6.67 (d, $J = 6.8$ Hz, 1H), 7.42 (d, $J = 6.8$ Hz, 1H); ^{13}C NMR ($CDCl_3$+CCl_4+DMSO-d_6, 100 MHz) δ: 7.8, 30.1, 65.2, 72.1, 102.4, 119.1, 134.8, 150.1, 159.1, 172.7; ESI-MS (*m*/*z*): 210 $(M+1)^+$, 232 $(M+Na)^+$; Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.39; H, 5.34; N, 6.73.
12. Comins, D. L.; Hao, H.; Saha, J. K.; Gao, J. *J. Org. Chem.* **1994**, *59*, 5120.