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Formal synthesis of (±)-camptothecin via tricyclic lactone as key synthon

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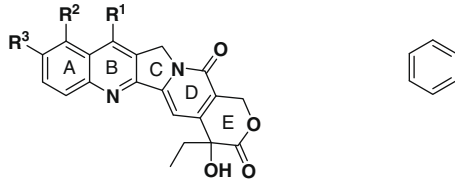
ABSTRACT

Formal synthesis of (±)-camptothecin via CDE tricyclic lactone employing tandem Michael addition, Dieckmann condensation and addition–elimination reaction as key steps starting from glycinate is described.

Camptothecin **1**, isolated from the Chinese plant *Camptotheca acuminata* by Wall and Wani in 1966,[1] elicited extensive interest due to its potent antitumor activity. The initial excitement quickly waned, because of problems associated with its insolubility and toxicity.[2] Liu and co-workers in 1985 reported that camptothecin had an unique mechanism of action that concerned selective inhibition of DNA topoisomerase I.[3] This disclosure served to regenerate interest in camptothecinoids and has led to the development of its analogues viz. topotecan[4] (Hycamtin) **2** and irinotecan[5] (Camptosar) **3** which are marketed as anticancer drugs. While one of its analogues foetidine **4** exhibits anti-HIV activity,[6] others are in different stages of clinical trials.[7]

Due to its excellent biological activity many research groups are attracted to synthesise camptothecin[8,9] and its analogues. However, most of the reported syntheses have drawbacks, involving lengthy routes and/or expensive starting materials, hazardous reagents or tedious reaction conditions and/or proceed in low overall yields. To overcome these problems there still exists a need to develop simple, practical and efficient process for the synthesis of camptothecin.

In keeping with our interest in the synthesis of camptothecin[9b,c,f,10] and its analogues, we decided to undertake the synthesis of CDE tricyclic lactone **5** (Scheme 1) which is the most versatile synthon to access a variety of camptothecin derivatives. Synthetic approaches of the analogues have typically involved synthesis of suitably functionalised CDE-ring or DE-ring or precursors thereof, which was then coupled with appropriate counter parts. In this



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

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

3. Irinotecan R^1=Et, R^2=H, R^3=OCOPipPip,HCl $3H_2O$

4. Foetidine

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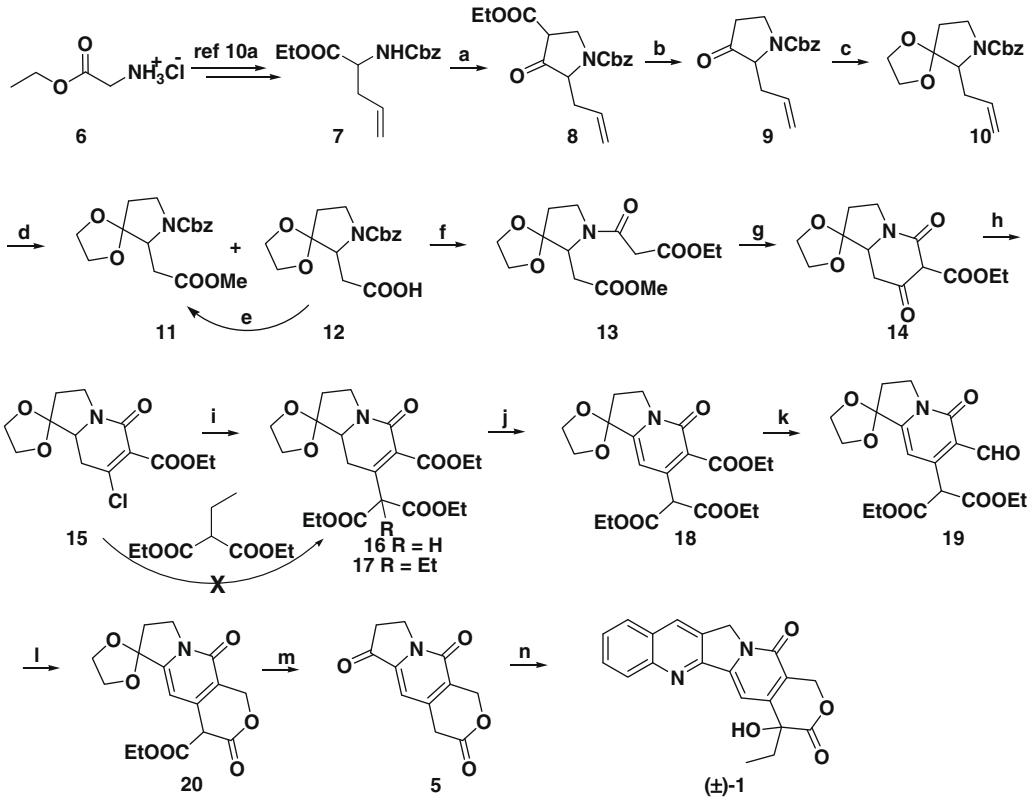

Scheme 1. Reagents and conditions: (a) NaH (1.2 equiv), ethyl acrylate (1.2 equiv), C_6H_6, rt 1 h, refluxed 2–3 h, 72%; (b) NaCl (4.0 equiv), DMSO–H_2O (3:1), 120–130 °C, 3 h, 78%; (c) 1,2-ethane diol, cat. PTSA, benzene, reflux, 8 h, 90%; (d) (i) OsO_4, acetone/water (3:1), $NaIO_4$, 3 h; (ii) oxone, methanol, rt, 16 h; (e) diazomethane, ether 0 °C–rt, 12 h, 95%; (f) (i) Pd/C, ethanol, 60 psi, 2 h; (ii) K_2CO_3, DCM, ethyl malonyl chloride, 0 °C–rt, 1 h, 88% (over two steps); (g) NaH, ethanol, rt, 3 h, 98%; (h) $POCl_3$, DCM, reflux, 4 h; (i) NaH, diethylmalonate, anhydrous benzene, rt, overnight, 65%; (j) DDQ, dioxane, reflux, 48 h, 98%; (k) DIBAL-H, THF, −60 °C, 2 h, 83%; (l) $NaBH_4$, methanol, 0 °C, 5 min 90%; (m) 10% HCl, 90–100 °C, 6 h, 82%; (n) Ref. 13.

Letter we wish to report a practical, simple and efficient synthesis of camptothecin via CDE skeleton which would have the flexibility to obtain the analogues of camptothecin from inexpensive, commercially available starting materials.

Synthesis started from urethane **7** as the starting material, which was prepared from glycinate **6**[10a] described by us. Urethane **7** was subjected to one-pot Michael addition, followed by Dieckmann cyclisation with ethyl acrylate using NaH as a base, to afford the keto ester **8** in 72% yield. Keto ester **8** was subjected to hydrolysis-decarboxylation under Krapcho conditions to afford the keto compound **9**, which was protected as acetal using ethylene glycol to afford urethane **10** in 90% yield. Urethane **10** was subjected to oxidative cleavage by using catalytic osmium tetraoxide followed by sodium periodate to afford an intermediate aldehyde. The crude aldehyde on treatment with oxone[11] in methanol at room temperature afforded ester urethane **11** in 60% yield along with acid **12** in 25% yield. Acid **12** was converted into required methyl ester **11** on treatment with diazomethane in 95% yield.

To synthesise D ring, ester **11** was subjected to benzyl carbamate deprotection by using Pd/C at 60 psi pressure followed by condensation with ethyl malonyl chloride using K_2CO_3 as a base in anhydrous DCM to afford the amide **13** in 88% yield over two steps**.** Amide **13** was treated with sodium hydride in ethanol at 0 °C to yield the cyclised compound in 98% yield, which existed in the keto form **14**. The keto compound **14** without purification was treated with $POCl_3$ in anhydrous dichloromethane at reflux temperature to furnish chloro compound **15.**

The resulting chloro compound **15** being unstable was immediately subjected to addition elimination reaction with diethyl 2-ethylmalonate, it did not furnish the desired product. However, the reaction of diethyl malonate using sodium hydride as the base in anhydrous benzene at room temperature overnight afforded the desired compound **16** in 65% yield. Aromatisation of **16** was achieved by employing DDQ as the oxidant in refluxing dioxane to furnish pyridone **18** in 98% yield. The next task was to selectively reduce hetero aromatic ester to aldehyde. Earlier[10a] we have shown that although this type of transformation could be readily accomplished by use of DIBAL-H, it may be pointed out that in a related study conducted recently[12] towards the synthesis of DE synthon of camptothecin, the aliphatic ester was preferentially reduced along with reduction of pyridone ring. It was therefore heartening to note that when the aromatic ester in pyridone **18** was subjected to selective reduction using 3 equiv of DIBAL-H in THF as a solvent at −60 °C, it afforded the desired aromatic aldehyde **19** in 83% yield. Aldehyde **19** on further treatment with sodium borohydride in THF/H_2O (9:1) at 0 °C furnished the lactone **20** in 90% yield. Acetal deprotection, ester hydrolysis and decarboxylation was carried out in one-pot by refluxing lactone **20** with 10% HCl for 6 h to afford the CDE tricyclic lactone **5** in 82% yield. The spectral data of compound **5** were in complete agreement with reported data.[13,14] Since **5** was also an intermediate in Shamma's synthesis of camptothecin **1**,[13] this constitutes a formal synthesis of camptothecin.

In conclusion we have described formal synthesis of (±)-camptothecin via tricyclic lactone employing simple reaction conditions and from cheap, commercially available starting material with an overall yield of 12.1%.

Acknowledgements

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14. NMR data for selected compound.
    Compound **16** ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.25–1.38 (m, 9H), 2.04–2.08 (m, 2H), 2.47 (dd, J = 16.8 and 5.05, 1H), 2.66 (dd, J = 13.7 and 16.8 Hz, 1H), 3.48–3.74 (m, 2H), 3.86 (dd, J = 13.7 and 5.05 Hz, 1H), 3.94–4.03 (m, 4H), 4.19–4.38 (m, 6H), 4.77 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 13.85, 13.87, 13.9, 25.8, 33.5, 41.9, 55.0, 59.5, 61.6, 62.10, 62.17, 65.2, 113.4, 130.8, 143.2, 159.5, 164.7, 165.7, 166.3 ppm. MS (ESI) m/z: 448 $(M+Na)^+$.
    Compound **18** ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.28 t, J = 7.20 Hz, 6H), 1.38 (t, J = 7.07, 3H), 2.39 (t, J = 6.95, 2H), 4.18–4.30 (2q, J = 7.20, 4H), 4.41 (q, J = 7.07, 2H), 4.09–4.17 (m, 6H), 4.88 (s, 1H), 6.47 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 13.8, 14.0, 33.5, 45.0, 54.4, 61.7, 62.2, 65.5, 100.0, 112.8, 124.7, 144.8, 149.6, 157.9, 165.4, 166.3 ppm. MS (ESI) m/z: 424 $(M+H)^+$, 446 $(M+Na)^+$.
    Compound **19** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.28 (t, J = 7.2, 6H), 2.43 (t, J = 6.7, 2H), 4.12–4.18 (m, 6H), 4.24 (q, J = 7.2, 4H), 6.08 (s, 1H), 6.39 (s, 1H), 10.47 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.9, 33.4, 45.1, 52.9, 62.1, 65.7, 101.1, 113.0, 121.5, 150.1, 154.0, 161.9, 166.9, 192.1 ppm. MS (ESI) m/z: 380 $(M+H)^+$, 402 $(M+Na)^+$.
    Compound **5** ^{1}H NMR ($CDCl_3$ + CCl_4, 400 MHz): δ 2.97 (t, J = 6.7, 2H), 3.66 (s, 2H), 4.35 (t, J = 6.7, 2H), 5.44 (s, 2H), 6.75 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 33.6, 34.1, 42.1, 66.2, 102.5, 126.6, 139.6, 142.4, 157.7, 167.2, 195.8 ppm. MS (ESI) m/z: 219 $(M)^+$, 242 $(M+Na)^+$.