

# Tandem Aza-Michael-Condensation–Aldol Cyclization Reaction: Approach to the Construction of DE Synthon of (±)-Camptothecin

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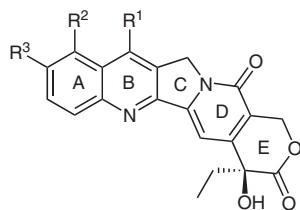
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**Abstract:** An efficient synthesis of the DE ring of camptothecin, employing a Reformatsky and a tandem one-pot, three-step transformation involving aza-Michael reaction, condensation with ethyl malonyl chloride followed by intramolecular ‘aldol’ reaction to furnish the dihydropyridone derivative from commercially available starting materials, has been achieved.

**Key words:** natural products, alkaloids, antitumor, Aldol cyclizations, Reformatsky reaction

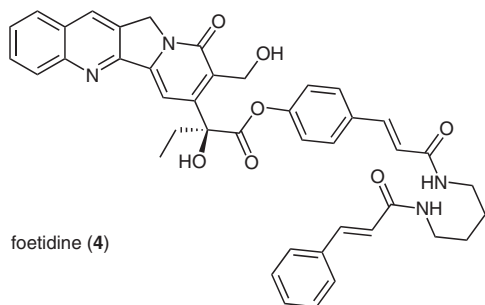
Camptothecin (**1**, Figure 1) is a well-known pentacyclic alkaloid, which was first isolated from *Camptotheca acuminata* by Wall and Wani in 1966.<sup>1</sup> Camptothecin and its analogues, collectively named camptothecins, have been isolated from various plant species<sup>2</sup> and show potent antitumor activity. The primary cellular target of camptothecin is the covalent binary complex formed between DNA and topoisomerase I during the process of DNA relaxation, and the stabilization of this complex by camptothecin is believed to lead to cell death.<sup>3</sup>



camptothecin (**1**) R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> = H

topotecan (**2**) R<sup>1</sup> = H, R<sup>2</sup> = CH<sub>2</sub>NMe<sub>2</sub>·HCl, R<sup>3</sup> = OH

irinotecan (**3**) R<sup>1</sup> = Et, R<sup>2</sup> = H, R<sup>3</sup> = OCOPipPip·HCl·3H<sub>2</sub>O



foetidine (**4**)

**Figure 1**

The initial exhilaration about camptothecin rapidly diminished due to a problem associated with its lower solubility and toxicity. But due to its excellent antitumor activity and unique mechanism of action, regenerated interest in camptothecins led to the development of its analogues topotecan<sup>4</sup> and irinotecan,<sup>5</sup> which are marketed as anti-cancer drugs. While one of its analogues, foetidine (**4**), exhibits anti-HIV activity,<sup>6</sup> others are in different stages of clinical trials.<sup>7</sup>

Several total syntheses of camptothecin<sup>8</sup> and its analogues have been achieved. 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.

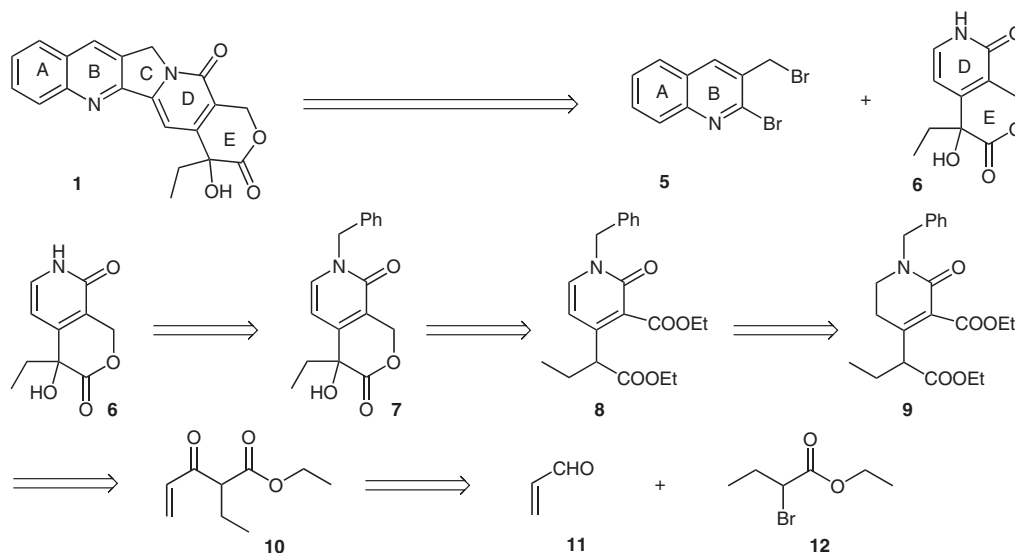
To overcome these problems there still exists need to develop a simple, practical, and efficient process for the synthesis of camptothecin.

As a part of our interest in developing an expedient synthesis of this unique molecule possessing excellent biological activity and challenging pentacyclic structure, we have directed our efforts towards developing a practical and efficient synthesis of camptothecin and its analogues.<sup>9</sup>

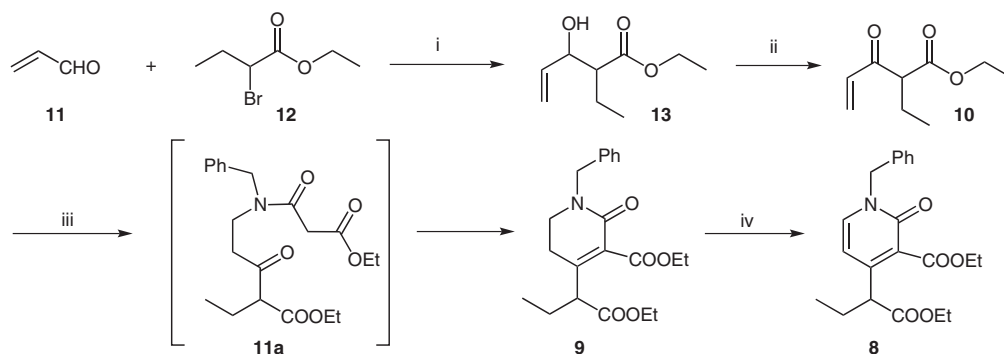
Herein we report a practical synthesis of the DE synthon of camptothecin which involves Reformatsky reaction and a tandem one-pot aza-Michael reaction and condensation with ethyl malonyl chloride followed by intramolecular cyclization to furnish dihydropyridone starting from inexpensive commercially available starting materials such as acrolein, ethyl bromobutyrate, and benzylamine (Scheme 1).

According to the proposed retrosynthetic path (Scheme 1), compound **10** can be prepared by utilizing the Reformatsky reaction. Thus acrolein **11** reacted with ethyl-2-bromo butyrate (**12**) in the presence of zinc and a catalytic amount of iodine in refluxing THF to afford β-hydroxy ester **13** in 67% yield (Scheme 2). The β-hydroxy ester **13** was oxidized with Jones reagent or IBX to give the required α,β-unsaturated ketone **10** in 85 and 90% yield, respectively.

With the α,β-unsaturated ketone **10** in hand, it was subjected to Michael addition with benzyl amine in CH<sub>2</sub>Cl<sub>2</sub> as the solvent. As soon as the starting material was completely consumed (TLC), K<sub>2</sub>CO<sub>3</sub> was added followed by ethyl malonyl chloride at 0 °C, and the reaction mixture was stirred at room temperature for eight hours to afford dihy-



Scheme 1



**Scheme 2** Reagents and conditions: i) Zn (3 equiv), iodine (cat.), THF, reflux, 8 h, 67%; ii) Jones reagent, acetone, 0 °C to r.t., 85%, IBX, EtOAc, reflux, 4 h, 90%; iii) BnNH<sub>2</sub> (1 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 0.5 h, K<sub>2</sub>CO<sub>3</sub>, (4 equiv), CH<sub>2</sub>Cl<sub>2</sub>, ethyl malonyl chloride (1.1 equiv), 8 h, 70%; iv) DDQ (1.1 equiv), dioxane, reflux, 24 h, 92%.

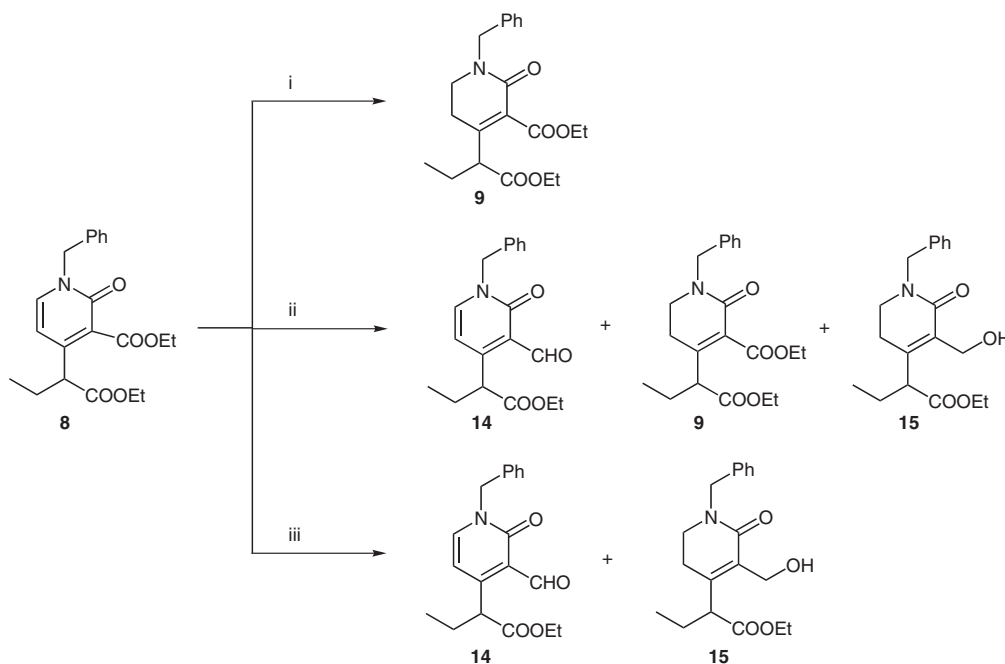
dropyridone **9** in 70% yield. It is noteworthy that the synthesis of **9**, which involves a tandem three-step transformation – viz. aza-Michael addition, condensation with ethyl malonyl chloride, and cyclization, was achieved in one pot. We isolated compound **11a** which was characterized by <sup>1</sup>H NMR spectroscopy. The analysis showed that **11a** exists as a mixture of rotamers. Compound **9** was subjected to aromatization employing DDQ as an oxidant in refluxing dioxane to furnish pyridone **8** in 92% yield.<sup>14</sup>

With diester **8** in hand, the next goal was to build a lactone ring by selective reduction of the heteroaromatic ester described earlier by us.<sup>9a</sup> Accordingly, ester **8** was subjected to reduction using DIBAL-H under the reaction conditions previously described. Surprisingly, treatment of **8** with three equivalents of DIBAL-H at –60 °C in THF furnished the required aldehyde **14** along with overreduced product (alcohol **15**) in a 1:3 ratio. In order to get aldehyde **14** exclusively, we varied the reaction conditions. Accordingly, ester **8** was subjected to treatment with one equivalent of DIBAL-H which surprisingly led to the formation of **9**,<sup>14,15</sup> where one of the double bond of pyridone was re-

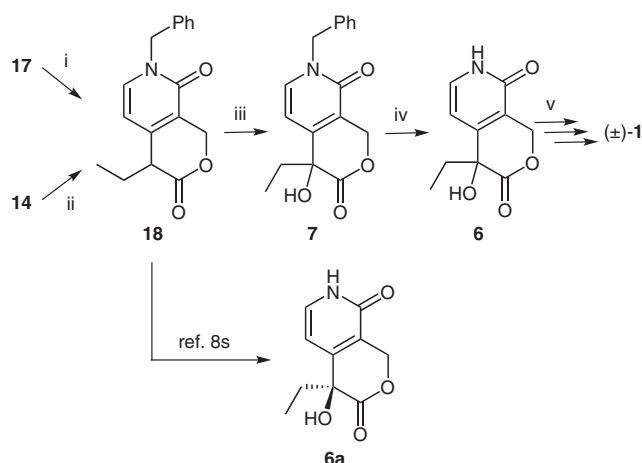
duced in 80% yield. The use of two equivalents of DIBAL-H at –60 °C led to the formation of a mixture of products (Scheme 3). Our efforts to get aldehyde **14** as the sole product were unsuccessful. Aldehyde **14** on reduction with NaBH<sub>4</sub> resulted in the formation of lactone **18** in 93% yield via the intermediacy of the corresponding alcohol, which underwent facile intramolecular transesterification (Scheme 4).

To overcome the problems encountered in the reduction of the pyridine ester with DIBAL-H, lactone **18** was alternatively synthesized from diester **8**. The exhaustive hydrolysis of diester **8** using excess lithium hydroxide in ethanol at room temperature furnished diacid **16** in 80% yield. The selective monoesterification of aliphatic acid in the presence of aromatic acid was achieved using nickel chloride as a catalyst in refluxing methanol for 12 hours and afforded ester **17** in 76% yield<sup>10</sup> (Scheme 5).

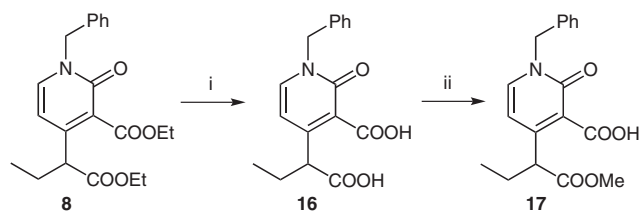
Monoacid **17** was then subjected to treatment with methyl chloroformate in THF at 0 °C to form mixed anhydride whose subsequent reduction with NaBH<sub>4</sub> led to the formation of an alcohol which underwent spontaneous lactonization to furnish lactone **18** in 84% yield<sup>11</sup> (Scheme 4).



**Scheme 3** Reagents and conditions: i) DIBAL-H (1 equiv), THF,  $-60^{\circ}\text{C}$ , 1.5 h, 80%; ii) DIBAL-H (2 equiv), THF,  $-60^{\circ}\text{C}$ , 2 h; iii) DIBAL-H (3 equiv), THF,  $-60^{\circ}\text{C}$ , 2 h.



**Scheme 4** Reagents and conditions: i) a)  $\text{Et}_3\text{N}$  (1.0 equiv), methylchloroformate (1.0 equiv), anhyd THF,  $0^{\circ}\text{C}$ , 1 h; b)  $\text{NaBH}_4$  (4.0 equiv),  $-78^{\circ}\text{C}$  3 h, 10% HCl, r.t., 12 h, 84%; ii)  $\text{NaBH}_4$  (1 equiv), THF– $\text{H}_2\text{O}$  (10:1), 30 min, 10% HCl, 93%; iii)  $\text{CuCl}_2$  (4.0 equiv),  $\text{Me}_2\text{NH}$ ,  $\text{O}_2$ , DMF, r.t., 24 h, 92%; iv)  $\text{Pd}(\text{OH})_2$ ,  $\text{H}_2$ , EtOH,  $50^{\circ}\text{C}$ , 5 h, 72%; v) ref. 13.



**Scheme 5** Reagents and conditions: i) excess  $\text{LiOH}$ , EtOH, r.t., 24 h, 80%; ii)  $\text{NiCl}_2$  (0.1 equiv), MeOH, reflux, 12 h, 76%.

Lactone **18** on reaction with  $\text{CuCl}_2$  and catalytic amounts of dimethyl amine under oxygen atmosphere afforded  $\alpha$ -hydroxy lactone **7** in 92% yield (Scheme 4).<sup>12</sup> The N-debenzylation was effected employing catalytic amounts of palladium hydroxide in ethanol at  $50^{\circ}\text{C}$  and furnished the desired DE-ring synthon **6** in 72% yield. This synthon **6** is the same common intermediate in Comins synthesis of camptothecin, and its spectral properties were in agreement with those reported by Comins<sup>13,14</sup> and by us.<sup>9f</sup>

In conclusion, we have achieved a synthesis of the (±)-DE synthon of camptothecin (**1**) in 13% overall yield utilizing tandem mild and efficient reaction conditions from commercially available and cheap starting materials. This route and its reaction conditions offer a practical synthetic route for camptothecin and its analogues.

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#### Spectral Data

Compound **8**:  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 0.90 (t,  $J$  = 7.4 Hz, 3 H), 1.24 (t,  $J$  = 7.1 Hz, 3 H), 1.40 (t,  $J$  = 7.3 Hz, 3 H), 1.70–1.81 (m, 1 H), 1.92–2.04 (m, 1 H), 3.5 (t,  $J$  = 7.4 Hz, 1 H), 4.13 (q,  $J$  = 7.1, 2 H), 4.45 (q,  $J$  = 7.3 Hz, 2 H), 5.09 (d,  $J$  = 14.4 Hz, 1 H), 5.17 (d,  $J$  = 14.4 Hz, 1 H), 6.28 (d,  $J$  = 7.2 Hz, 1 H), 7.24 (d,  $J$  = 7.2 Hz, 1 H), 7.29–7.35 (s, 5 H).

Compound **9**:  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 0.92 (t,  $J$  = 7.4 Hz, 3 H), 1.26 (t,  $J$  = 7.2 Hz, 3 H), 1.35 (t,  $J$  = 7.3 Hz, 3 H), 1.51–1.71 (m, 2 H), 1.82–1.96 (m, 1 H), 2.21–2.50 (m, 1 H), 3.22–3.42 (m, 2 H), 3.60–3.73 (m, 1 H), 4.15 (q,  $J$  = 7.2 Hz, 2 H), 4.36 (q,  $J$  = 7.3 Hz, 2 H), 4.49 (d,  $J$  = 14.7 Hz, 1 H), 4.66 (d,  $J$  = 14.7 Hz, 1 H), 7.24–7.30 (m, 5 H).

Compound **14**:  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 0.96 (t,  $J$  = 7.4 Hz, 3 H), 1.24 (t,  $J$  = 7.1 Hz, 3 H), 1.60–1.77 (m, 1 H), 1.92–2.10 (m, 1 H), 4.13 (q,  $J$  = 7.1 Hz, 2 H), 4.96 (t,  $J$  = 7.3 Hz, 1 H), 5.13 (s, 2 H), 6.30 (d,  $J$  = 7.2 Hz, 1 H), 7.42 (d,  $J$  = 7.2 Hz, 1 H), 7.31–7.38 (m, 5 H), 10.52 (s, 1 H).

Compound **6**:  $^1\text{H}$  NMR (400 MHz;  $\text{CD}_3\text{OD}$ ):  $\delta$  = 0.93 (t,  $J$  = 7.3 Hz, 3 H), 1.86 (q,  $J$  = 7.2 Hz, 2 H), 5.22 (d,  $J$  = 16.2 Hz, 1 H), 5.41 (d,  $J$  = 16.2 Hz, 1 H), 6.63 (d,  $J$  = 6.8 Hz, 1 H), 7.46 (d,  $J$  = 6.8 Hz, 1 H).

#### (15) Typical Procedure for Compound 9

To a stirred solution of keto compound **10** (5 g, 29.4 mmol) in dry  $\text{CH}_2\text{Cl}_2$  benzyl amine (3.21 mL, 29.4 mmol) was added dropwise at r.t. and allowed to stir for 20 min. After the completion of the reaction (TLC),  $\text{K}_2\text{CO}_3$  (14.2 g, 102.9 mmol) was added followed by dropwise addition of ethyl malonyl chloride (4.89 mL, 38.22 mmol) at 0 °C. The mixture was stirred at r.t. until completion (1 h, TLC), and then was filtered, and the residue was washed with  $\text{CH}_2\text{Cl}_2$  (3  $\times$  30 mL). The organic layer was washed with  $\text{H}_2\text{O}$ , brine, dried over anhyd  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated on a rotary evaporator under diminished pressure. The resulting residue was purified by flash column chromatography (silica gel) using EtOAc–PE (3:7) as an eluent, affording the dihydropyridone **9** as a colorless liquid (7.6 g, 70% yield).

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