Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 6879–6882
Tetrahedron Letters

# Formal total synthesis of camptothecin via ring-closing metathesis strategy☆

Subhash P. Chavan,* K. Pasupathy, M. S. Venkatraman and Ramesh R. Kale

*Division of Organic Chemistry: Technology, National Chemical Laboratory, Pune 411008, India*

Received 17 May 2004; revised 14 July 2004; accepted 22 July 2004

**Abstract**—A formal total synthesis of camptothecin **1** is presented. The key steps include construction of the D-ring of camptothecin featuring an efficient ring-closing metathesis (RCM) reaction and the subsequent Michael addition of nitropropane across the double bond of the dihydropyridone **3**.


Camptothecin, a pentacyclic alkaloid isolated from the Chinese tree *Camptotheca acuminata* by Wall et al. in 1966,[1] is one of the outstanding lead compounds in anticancer drug development. Camptothecin and several analogues of camptothecin, collectively called camptothecins, have been isolated from various botanical sources. Very recently extracts from *Pyrenacantha klaineana*[2] and the hairy roots of *Ophiorrhiza pumila*[3] have yielded camptothecins. Camptothecin as such was not ideal for pharmaceutical development, mostly due to its toxicity, poor solubility and the unstable nature of the lactone ring, which opens rapidly to an inactive hydroxy acid under physiological conditions. Liu and co-workers reported in 1985 that the cytotoxicity of camptothecin was attributed to a unique mechanism of action involving selective inhibition of DNA topoisomerase I, an enzyme essential for relaxation of DNA during important cellular process.[4] This sparked renewed interest in camptothecins, culminating in the launch of two successful compounds, namely irinotecan and topotecan (Fig. 1) in clinical practice. Several other compounds are in various stages of clinical trials.[5]

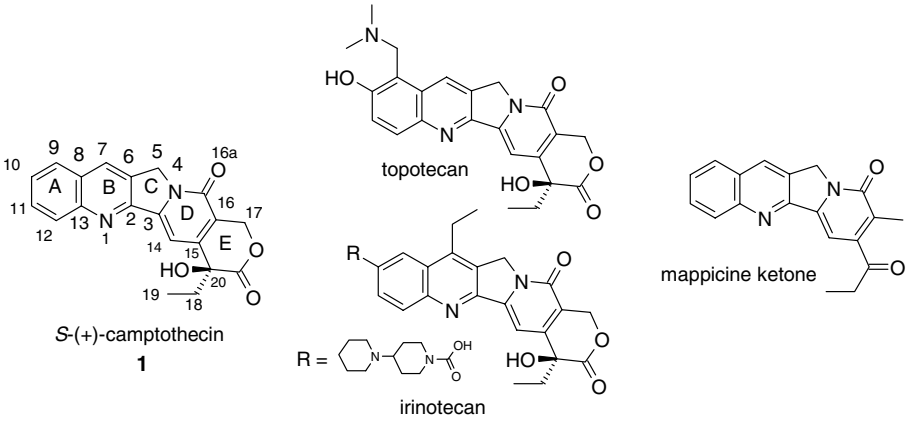
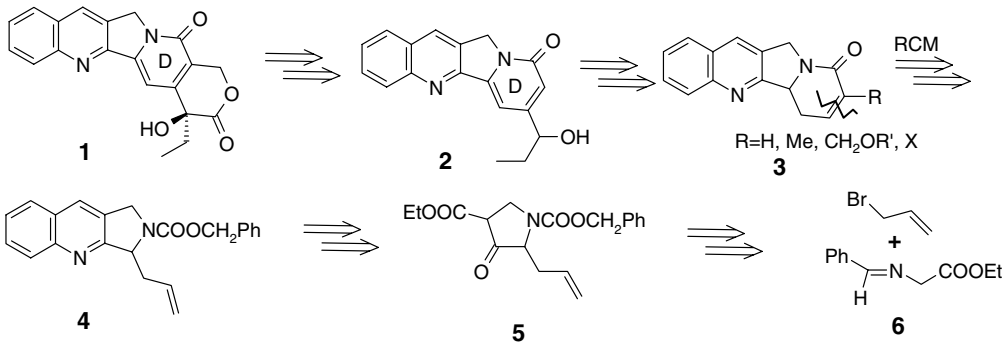



**Figure 1.**

*Keywords*: Anticancer; Camptothecin; Ring-closing metathesis (RCM); Pyridone.
☆ Presented at the 5th National Symposium in Chemistry (CRSI-5) held during February 8–10, 2003 at CLRI Chennai, India.
* Corresponding author. Tel.: +91-25893300 2289; fax: +91-2025893614; e-mail: spchavan@dalton.ncl.res.in

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.07.101



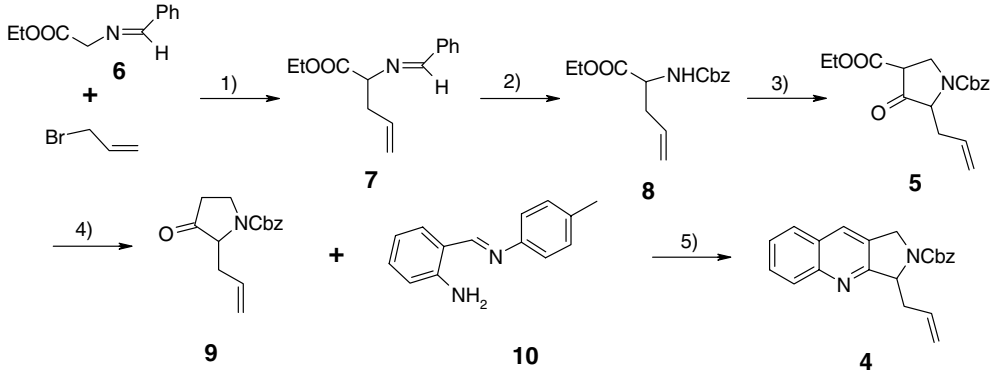

**Scheme 1.**

It has been shown that changing the six-membered α-hydroxy lactone ring found in camptothecin to a seven-membered β-hydroxy lactone ring reinforces the stability of the lactone thereby reducing its conversion into the inactive carboxylate form. Homocamptothecin has been shown to be much more active than the parent compound against a variety of tumour cells.[6] Camptothecin also demonstrates impressive antiretroviral activity against acute and chronic HIV-1 infections.[7]

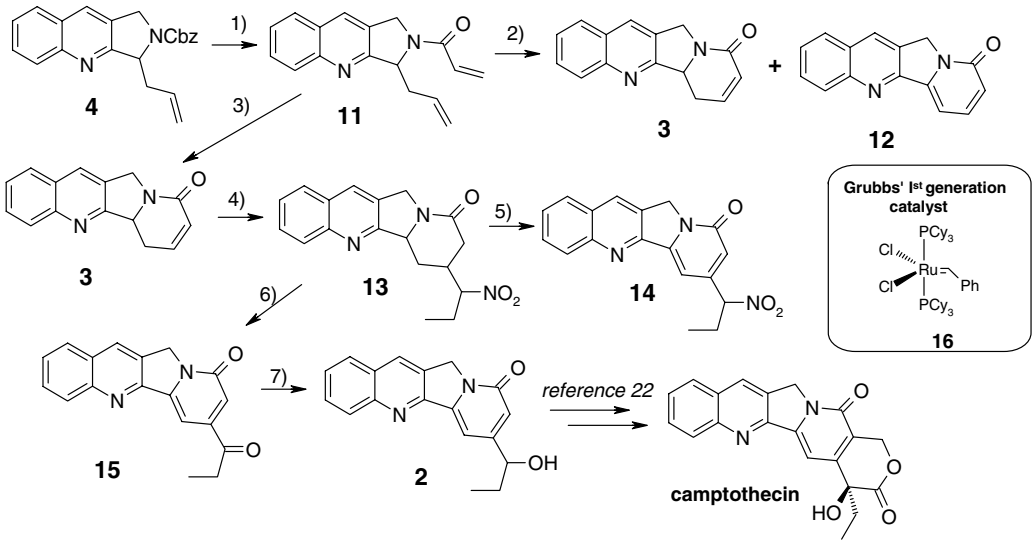
Due to the excellent biological activity, unique mode of action and challenging structure, camptothecin has been a popular compound over four decades for both medicinal as well as synthetic chemists. Several total syntheses have been developed as a direct and practical route to the preparation of analogues and for scale-up.[8] As a part of our research program, we have directed our efforts towards a practical and efficient synthesis of camptothecin and mappicine ketone. Our first approach, described in 1998,[9] involved an intramolecular Michael reaction for the construction of the pyridone D-ring. In another approach, we utilised an intramolecular aldol condensation of an appropriate ketol for the construction of the D-ring of camptothecin[10a] (Scheme 1).

Our continuing interest in camptothecin and mappicine ketone[10b] led us to explore a new and efficient approach for the synthesis of the D-ring utilising intramolecular ring-closing metathesis (Scheme 2). This paper presents our detailed investigation of attempts to transform the envisioned strategy into reality.

Accordingly, the versatile tricyclic amine **4** was synthesised (Scheme 2) starting from a very simple Schiff's base **6**. Alkylation of **6** with allyl bromide under phase transfer conditions ($TBAHSO_4$ as phase transfer catalyst) using 10% aq NaOH furnished the allylated Schiff's base **7** in excellent yield. Acidic hydrolysis of **7** liberated the free amine, which in turn was protected as carbamate **8** using CbzCl in 96% yield from **7**. To our delight urethane **8** underwent a one-pot Michael addition, followed by Dieckmann cyclisation with ethyl acrylate using NaH as base, to afford the keto ester **5** in 65% yield. Keto ester **5** when subjected to hydrolysis and decarboxylation using 10% HCl at reflux temperature for 5 h provided the ketone **9**. The same transformation was also achieved by following Krapcho' s decarboxylation protocol (DMSO, NaCl, 125 °C, 4 h, 64% yield from **8**).[10c] Compound **9** without purification was subjected to modified Friedlander condensation with the Schiff's base **10** to provide the desired quinoline **4** in 72% yield. Deprotection of the Cbz group of **4** was performed with 10 equiv of TMSCl/NaI at 0 °C—rt for 1 h using $CH_3CN$ as the solvent.[11] The same transformation was also efficiently achieved with 16 equiv of KOH in ethanol at reflux.[12] This was followed by direct acylation with acryloyl chloride in the presence of $K_2CO_3$ to furnish the acrylamide **11** in 73% yield from urethane **4**. A consistent and higher yield of acrylamide **11** was obtained




**Scheme 2.** Reagents and conditions: (1) 10% NaOH, $TBAHSO_4$, DCM, rt, 0.5 h, 97%; (2) (a) 10% HCl, rt, 0.5 h, 94%, (b) CbzCl, $K_2CO_3$, DCM, rt, 3 h, 96%; (3) NaH, $C_6H_6$, ethyl acrylate, reflux, 3 h, 65%; (4) 10% HCl, reflux, 5 h; (5) toluene, PTSA, reflux, 8 h, 72%.




**Scheme 3.** Reagents and conditions: (1) (a) KOH, EtOH, reflux, 24 h; (b) acryloyl chloride, $K_2CO_3$, DCM, rt, 3 h, 73%; (2) **16** (10 mmol%), benzene, reflux, 26 h, 80%; (3) Ti(O*i*Pr)$_4$, DCM, **16** (10 mmol%), reflux, 16–20 h, 89%; (4) nitropropane, DBU, rt, 16 h, 86%; (5) DDQ, dioxane, reflux, 5 h, 25%; (6) NaOH, MeOH, rt, 3 h, Concd HCl, 0 °C, 1 h and rt, 12 h, 23%; (7) $NaBH_4$, MeOH, 0 °C, 1 h, 99%.

when the Cbz group in **4** was obtained under alkaline conditions (Scheme 3).

Having synthesised the required substrate **11**, the stage was now set for evaluating the construction of the D-ring via a ring-closing metathesis protocol. It was very gratifying to find that when the amide **11** was refluxed in benzene employing Grubbs first generation catalyst **16**[13] for 26–32 h under nitrogen, along with the desired dihydropyridone **3**, the completely aromatised tetracyclic pyridone **12** was also obtained. The products **3** and **12** were formed in the ratio 3:2 ($^1$H NMR analysis), respectively. Performing the RCM employing Marco's protocol[14] circumvented this shortcoming, giving the desired dihydropyridone **3** in 89% yield. Tetrahydropyridone **3** is the key intermediate in Stork's synthesis of camptothecin.[15] Having four out of the five rings of camptothecin in place, we explored the possibility of functionalising the fifth ring of camptothecin by conjugate addition. It was observed that a mixture of DBU, nitropropane and **3** at room temperature afforded nitro compound **13** in a very high yield. It is pertinent to mention that similar Michael additions of nitroalkanes promoted by DBU have been documented on α,β-unsaturated lactams where activation of the double bond is a prerequisite, and achieved by placing electron-withdrawing groups on the nitrogen[16,17] or by converting the lactam into a thiolactam.[18] The scope of this transformation is under investigation and will be described in due course.

Even though the DDQ oxidation of the nitrolactam **13** afforded the desired pyridone **14**, the poor yield of this transformation was a cause for concern. However, our attempts to improve the yields by increasing the relative quantity of the reagent and the reaction time were unsuccessful. Therefore we decided to perform the Nef reaction on **13** prior to the dehydrogenation procedure. On exposure to standard Nef conditions,[19] not only was the nitro functionality transformed to a carbonyl, but surprisingly oxidation to the corresponding pyridone **15** was also effected in 23% yield. However, optimum conditions for this transformation have not been extensively studied [conditions attempted are (a) NaOH, MeOH, −44 °C, 3 h, followed by $H_2SO_4$, MeOH, −20 °C to 0 °C, 4 h; (b) $K_2CO_3$, 30% $H_2O_2$, MeOH, rt, 8 h;[20] (c) NaOH, $Na_2HPO_4$, MeOH, rt, 1 h, followed by Oxone, rt, overnight[21]]. Finally the reduction of the carbonyl group of **15** with $NaBH_4$ gave the desired hydroxy pyridone **2** in nearly quantitative yield. Hydroxy compound **2** is a key intermediate in Murata's synthesis of camptothecin,[22] thus, our approach constitutes a formal total synthesis of camptothecin.

In summary we have established the efficacy of a RCM reaction in the construction of pyridone moiety of the antitumour alkaloid camptothecin **1**. Further application of this strategy towards the synthesis of alkaloids related to camptothecin, viz. mappicine ketone, is currently underway in our laboratory.

## Acknowledgements

Authors K.P. and M.S.V. thank CSIR New Delhi for fellowships and funding from DST, New Delhi (R.R.K thanks DST for a fellowship).

## 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. Hecht, S. M.; Newman, D. J.; Kingston, D. G. I. *J. Nat. Prod.* **2000**, *63*, 1273–1276.
3. Kitajima, M.; Yoshida, S.; Yamagata, K.; Nakamura, M.; Takayama, H.; Saito, K.; Sekib, H.; Aimi, N. *Tetrahedron* **2002**, *58*, 9169–9178.

4. (a) Hsiang, Y. H.; Hertzberg, R.; Hecht, S.; Liu, L. F. *J. Biol. Chem.* **1985**, *260*, 14873–14878; (b) Hsiang, Y. H.; Liu, L. F. *Cancer Res.* **1998**, *48*, 1722–1726.
5. Lerchen, H. G. *Drugs Future* **2002**, *27*, 869–878, and references cited therein.
6. Lavergne, O.; Lesur-Ginot, L.; Rodas, F. P.; Bigg, D. C. H. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2235–2238.
7. Priel, E.; Showalter, S. D.; Blair, D. G. *AIDS Res. Hum. Retroviruses* **1991**, *7*, 65–72.
8. Selected reviews on camptothecin and related alkaloids including their synthesis: (a) Cragg, G. M.; Newman, D. J. *J. Nat. Prod.* **2004**, *67*, 232–234; (b) Oberlies, N. H.; Kroll, D. J. *J. Nat. Prod.* **2004**, *67*, 129–135; (c) Du, W. *Tetrahedron* **2003**, *59*, 8649–8687; (d) Baurle, S.; Koert, U. In *Organic Synthesis Highlights IV*; Schmalz, H.-G., Ed.; Wiley–VCH: Weinhiem, 2000; pp 232–240; (e) Takayama, H.; Kitajima, M.; Aimi, N. *J. Synth. Org. Chem.* **1999**, *57*, 181; (f) Kawato, Y.; Terasawa, H. *Prog. Med. Chem.* **1997**, *34*, 69–109; (g) *Camptothecins: New Anticancer Agents*; Potmesil, M., Pinedo, H. M., Eds.; CRC: Boca Raton, FL, 1995; (h) Wall, M. E.; Wani, M. C. In *The Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed.; Wiley: London, 1994; pp 689–713; (i) Curran, D. P.; Sisko, J.; Yeske, P. E.; Liu, H. *Pure Appl. Chem.* **1993**, *65*, 1153–1159; (j) Hutchinson, C. R. *Chem. Heterocycl. Compd.* **1983**, *25*, 753–781; (k) Cia, J. C.; Hutchinson, C. R. In *The Alkaloids Chemistry and Pharmacology*; Brossi, A., Ed.; Academic: New York, 1983; Vol. 21, pp 101–137; (l) Hutchinson, C. R. *Tetrahedron* **1981**, *37*, 1047–1065; (m) Schultz, A. G. *Chem. Rev.* **1973**, *73*, 385–405; (n) Wani, M. C.; Wall, M. E. *J. Org. Chem.* **1969**, *34*, 1364–1367.
9. Chavan, S. P.; Venkatraman, M. S. *Tetrahedron Lett.* **1998**, *39*, 6745–6748.
10. (a) Chavan, S. P.; Sivappa, R. *Tetrahedron Lett.* **2004**, *45*, 3113–3115; (b) Chavan, S. P.; Sivappa, R. *Tetrahedron Lett.* **2004**, *44*, 3941–3943; (c) Giles, M.; Hadley, M. S.; Gallagher, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1047–1048.
11. Olah, G. A.; Narang, S. C.; Balram Gupta, B. G.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247–1251.
12. Georgiev, V. S.; Smithers, D. A.; Shamma, M. *Tetrahedron* **1973**, *29*, 1949–1954.
13. For general reviews on RCM, see: (a) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley–VCH: Weinhiem, 2003; Vol. 1; (b) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley–VCH: Weinhiem, 2003; Vol. 2; (c) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29; (d) Furstner, A.; Liebl, M.; Lehmann, C. W.; Picquet, M.; Kunz, R.; Bruneau, C.; Touchard, D.; Dixneuf, P. H. *Chem. Eur. J.* **2000**, *6*, 1847–1857; (e) Furstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012–3043; (f) Herndon, J. W. *Coord. Chem. Rev.* **1999**, *181*, 177–242; (g) Philips, A. J.; Abell, A. D. *Aldrichim. Acta* **1999**, *32*, 75–89; (h) *Alkene Metathesis in Organic Synthesis*; Furstner, A., Ed.; Springer: Berlin, 1998; (i) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450; (j) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371–388; (k) Schuster, M. S.; Blechert, S. *Angew. Chem., Int. Ed.* **1997**, *36*, 2036–2056; (l) Hendson, J.; Furstner, A. *Top. Catal.* **1997**, *4*, 285–299.
14. Rodriguez, S.; Castillo, E.; Carda, M.; Marco, J. A. *Tetrahedron* **2002**, *5*, 1185–1192.
15. Stork, G.; Schultz, A. G. *J. Am. Chem. Soc.* **1971**, *93*, 4074–4075.
16. Hanessian, S.; Seid, M.; Nilsson, I. *Tetrahedron Lett.* **2002**, *43*, 1991–1994.
17. Willis, L. C.; Hately, M. J.; Crosby, S. R. *Tetrahedron Lett.* **2000**, *41*, 397–401.
18. Sosnicki, J. G.; Liebscher, J. *Synlett* **1996**, 117–118.
19. (a) Kloetzel, M. C. *J. Am. Chem. Soc.* **1948**, *70*, 3571; For a recent review on the Nef reaction see: (b) Ballini, R.; Petrini, M. *Tetrahedron* **2004**, *60*, 1017–1047.
20. Olah, G. A.; Arvanaghi, M.; Vankar, Y. D.; Surya Prakash, G. K. *Synthesis* **1980**, 662–663.
21. Zhou, B. N.; Hoch, J. M.; Johnson, R. K.; Mattern, M. R.; Eng, W. K.; Ma, J.; Ceccherelli, P.; Curini, M.; Marcotullio, M. C.; Epifano, F.; Rosati, O. *Synth. Commun.* **1998**, *28*, 3057–3064.
22. Murata, N.; Sughihara, T.; Kondo, Y.; Sakamoto, T. *Synlett* **1997**, 298–300.