Synthesis of (+)-camptothecin[#]

Subhash P. Chavan* and M. S. Venkatraman

Organic Chemistry: Technology: National Chemical Laboratory, Pune 411008, India
E-mail: spchavan@dalton.ncl.res.in

This paper is dedicated to Dr. A. V. Rama Rao on the ocassion of 70th birthday

(received 16 Sep 04; accepted 08 Jan 05; published on the web 15 Jan 05)

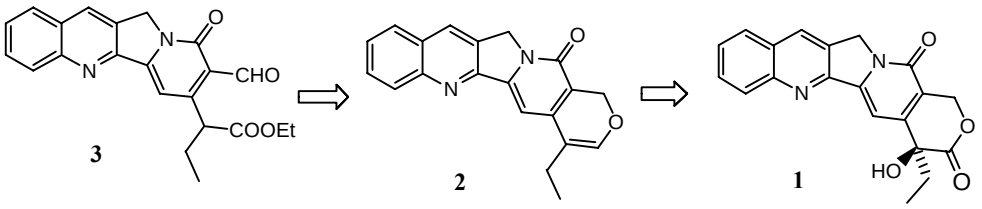
Abstract

A synthesis of optically pure camptothecin was achieved in 4 steps from previously reported aldehyde employing Sharpless asymmetric dihydroxylation as the key step.

Keywords: Camptothecin, anticancer, Sharpless asymmetric dihydroxylation

Introduction

Natural camptothecin **1** isolated from *Camptotheca acuminata decene* had an *S* configuration at C20. It is this *S* configuration that shows excellent anti-cancer activity.[1] Since the *R* isomer is inactive, any synthesis of camptothecin **1** would be more attractive if it furnishes it in an optically pure form. Several approaches have been employed to fix the desired stereochemistry at C20 which include Corey's[2] synthesis furnished camptothecin in optically pure form for the first time by employing a chemical resolution strategy using quinine as the resolving agent, asymmetric alkylation.[3] Comins's[3] synthesis employed nucleophilic addition of a suitably substituted pyridine anion to a ketoester to fix the desired stereochemistry at C20. However approach by Bennasar employs nucleophilic addition of enolate of ester to the pyridone of tetracyclic camptothecin framework.[4a] Very recently they have also accomplished the synthesis of optically active camptothecin employing the same strategy. [4b] Tagami *et al* recently reported[5a] the quenching of the anion derived by treating deoxycamptothecin using LiHMDS, with Davis's chiral oxaziridine to furnish *S*- (+)-camptothecin with moderate *ee*.

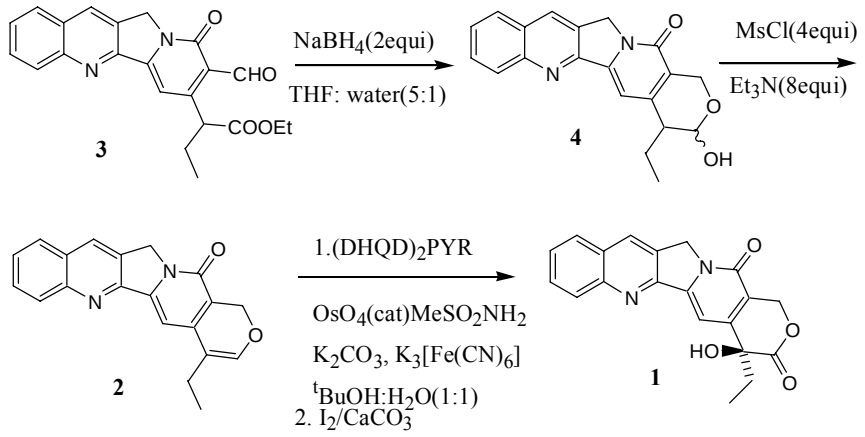


Scheme 1

Tagawa *et al*[5b,5c] employed the diastereoselective ethylation of indolizine derivatives using *N*-substituted (*R*)-proline as a stereo controlling unit Ciufolini *et al*[6a] used an enzymatic hydrolysis of meso diester to provide a chiral α-hydroxy acid, which was efficiently converted to camptothecin in several steps in high overall yields. Similarly, Henegar has reported[6b] multigram synthesis of camptothecin involving enzymatic resolution as the key step to establish the required chirality in the molecule. Almost all the above synthetic methods devoted towards optically active camptothecin invariably involve either chiral synthons or synthesis of chiral intermediates. Several syntheses have employed Sharpless asymmetric dihydroxylation[7, 8, 9] of enol ether followed by oxidation to provide α-hydroxy lactone (synthesis of E-ring) in optically pure form, but at the early stage of the synthesis. Since *S*-(+)-camptothecin possesses only one chiral centre, we thought of incorporating it at the end thereby attaining "chiral economy" (Scheme 1).

Results and Discussion

A few years ago we have accomplished the synthesis of (±)-camptothecin[10a] where chemoselective reduction with DIBAL-H provided us with aldehyde **3**,[10b] which, we thought, could be easily converted to the enol ether **2.** Based on our observation that the aldehyde **3** could be converted to lactol **4** on treatment with 2 equivalents of sodium borohydride, a Sharpless asymmetric dihydroxylation approach to (+)-camptothecin **1** was envisaged. Thus (Scheme 2), aldehyde **3** was treated with 2 equivalents of sodium borohydride in tetrahydrofuran and water (5:1) at 0^oC to yield lactol **4** in 90% yield. The lactol **4** was efficiently converted (92% yield) to the enol ether **2** using 4 equivalents of methanesulfonyl chloride[7] in the presence of 8 equivalents of triethyl amine in tetrahydrofuran as the solvent. Asymmetric dihydroxylation using Sharpless conditions[11] and using $(DHQD)_2$ PYR as the chiral ligand furnished the diol as mixture of diastereomers. The mixture was oxidized to the lactone using $I_2/NaHCO_3$[12] as the oxidizing agent to provide (+)-camptothecin **1** which was similar in all respects to the natural sample. $\{[\alpha]^{25}_D$ +39, (c= 0.165, $CHCl_3$: MeOH, 4: 1), lit.[3b] $[\alpha]^{25}_D$ +45, (c= 0.30, $CHCl_3$: MeOH, 4: 1).



Scheme 2

Thus we have demonstrated that *S*-(+)-camptothecin can be readily accessed by delaying the introduction of chirality towards the end by employing Sharpless dihydroxylation protocol on the pentacyclic enol ether.

Acknowledgments

MSV thanks CSIR for fellowship and funding from CSIR (New Delhi) under YSA (SPC) scheme is gratefully acknowledged.

Experimental Section

4-Ethyl-3hydroxy-3,4,12,14-tetrahydro-1*H*-pyrano[3',4',6,7]indolizino[1,2*b*]quinoline-14-one, (4). To 0.079 g (0.2 mmol) of aldehyde **3** in 5 ml THF and 1 ml water at 0°C was added 0.015 g (0.4 mmol) of $NaBH_4$ and the mixture allowed to stir at 0°C for 0.5 hr. 10% HCl was added and the mixture extracted with 2 x 25 ml of $CHCl_3$. The combined organic layer was dried over anhydrous sodium sulphate. Concentration under vacuo and purification by column chromatography over silica gel using 5% methanol in chloroform as eluent furnished lactol **4** 0.063 g (90% yield). mp. 212-214°C. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 1.1 (t, 3H); 1.7 (q, 2H); 2.7 (t, 1H); 4.85 (dd, 2H); 5.25 (s, 2H); 5.45 (s, 1H); 7.15 (s, 1H); 7.65 (t, 1H); 7.85 (t, 1H); 7.95 (d, 1H); 8.2 (d, 1H); 8.35 (s, 1H). **IR** (Neat): cm^{-1} 3400; 1660; 1600. **Mass** (m/e): 334 (7); 305 (15); 287 (10); 273 (17); 261 (10); 112 (20); 109 (20); 97 (25); 83 (40); 69 (65); 60 (53); 55 (100). **Analysis** Calculated for $C_{20}H_{16}N_2O_4$: C- 72.0; H- 5.1; N- 8.4. Observed: C- 71.83; H- 5.05; N- 7.96.

4-Ethyl-12,14-dihydro-1*H*-pyrano[3′,4′,6,7]indolizino[1,2*b*]quinoline-14-one, (2). To 0.06 g (0.17 mmol) of lactol **4** in 10 ml dry THF was added 0.145 g (1.4 mmol) of triethyl amine

followed by 0.082 g (0.7 mmol) of mesyl chloride at 0°C. The reaction mixture was stirred at room temperature for 24 h water was added and aqueous phase extracted with chloroform (3 x 15 ml). The combined organic phase was dried over anhydrous sodium sulphate. Concentration under vacuo followed by purification by column chromatography over silica gel using chloroform as eluent furnished enol ether **2** 0.052 g (92% yield). **^{1}H NMR** (200 MHz): δ 1.25 (t, 3H); 2.45 (q, 2H); 5.2 (s, 2H); 5.25 (s, H); 6.65 (s, 1H); 7.2 (s, 1H); 7.6 (t, 1H); 7.8 (t, 1H); 7.9 (d, 1H); 8.2 (d, 1H); 8.35 (s, 1H). **^{13}C NMR** (50 MHz): 13.7(q); 20.6(t); 49.7(t); 63.3(t); 95.5(d); 114.8(s); 115.6(s); 127.5(d); 127.9(d); 128.7 (s); 129.4(d); 130.2(d); 130.7(d); 143.5(s); 145.6(s); 146.9(d); 148.8(s); 153.6(s); 158.6(s). **IR** (Neat): cm^{-1} 1660; 1620; 1540; 1020. **Mass** (m/e): 316 (60); 301 (100); 287 (20); 273 (40); 259 (7); 243 (20); 122 (15). **Analysis** Calculated for $C_{20}H_{14}NO_3$: C- 75.9; H- 4.7; N- 8.9. Observed: C- 75.84; H- 5.09; N- 9.38

4(*S*)-4-Ethyl-4-hydroxy-1*H*-pyrano[3′,4′,6,7]indolizino[1,2*b*]quinoline-3,14(4H,12H)-dione, (1). 0.063 g (0.18 mmol) of potassium ferricyanide, 0.026 g (0.18 mmol), of potassium carbonate, 0.006 g (0.06 mmol) of methane sulphonamide was dissolved in 1 ml tertiary butanol and 1 ml water. To this slurry was added a precomplexed mixture of 0.005 g (0.0006 mmol) of $(DHQD)_2$ PYR and catalytic OsO_4 solution in 0.5 ml of t-butanol. The mixture was stirred for 10 min at 0°C. To the mixture at 0°C was added enol ether 0.020 g (0.06 mmol) in 1 ml tert-butanol. The mixture was stirred at 0°C for 7 hrs. The tert butanol was removed under reduced pressure and the mixture extracted with 5 x 10 ml portions of $CHCl_3$. The combined chloroform layer was washed with 10% HCl. The chloroform layer was dried over anhydrous sodium sulphate concentration furnished crude diol (0.016 g). The crude diol was dissolved in 10 ml methanol and 1 ml water. Calcium carbonate 0.145 g (0.57 mmol) was added followed by 0.140 g (0.57 mmol) of Iodine and the mixture stirred at room temperature for 24 hrs. The methanol was removed under *vaccuo.* The mixture was extracted with 10 x 10 ml portions of chloroform and the combined chloroform layer was dried over sodium sulphate. Concentration and purification by column chromatography over silica gel using 2% MeOH in chloroform furnished +**1** 0.007 g (33% yield). $[\alpha]^{25}_D$ +39 (c= 0.142, $CHCl_3$; MeOH 4:1), lit.[3b] $[\alpha]^{25}_D$ +45, (c= 0.30, $CHCl_3$: MeOH, 4: 1).

References

Presented at the sixth NOST Symposium held during April 20-23, 1997 at Lonavala, India.

1. (a) Wall, M. E.; Wani, M.C. In *Anticancer agents based on natural product models* Cassadt, J. M.; Donuros, J. D., Eds. Academic Press: New York, 1980, p 417. (b) Wall, M. E.; Wani, M.C. ; Cook, C. E.; Palmer, K. H.; McPhail, A. T. ; Sim, J. A. *J. Am. Chem. Soc.* **1966,** *88*, 3888. (c) Du, W. *Tetrahedron* **2003**, *59*, 8649 and references cited therein. (d) Lerchen, H. G. *Drugs Future* **2002**, *27*, 869 and references therein.
2. Corey, E. J.; Crouse, D. N.; Anderson, J.E. *J. Org. Chem.* **1975**, *40*, 2140.

3. (a) Comins, D. L.; Baevsky, M. F.; Hao, H. *J. Am. Chem. Soc.* **1992**, 114, 10971. (b) Comins, D. L.; Nolan, J. M. *Org. Letters*. **2001**, *3*, 4255 and references cited therein.
4. (a) Bennasar M.-L.; Juan C.; Bosch, *Chem. Comm.* **2000,** 2459. (b) Bennasar M.-L.; Zulaica, E.; Juan, C.; Alonso, Y.; Bosch, J. *J. Org. Chem.* **2002**, *67*, 7465.
5. (a) Tagami, K.; Nakazawa, N.; Sano, S.; Nagao, Y. *Heterocycles* **2000**, *53*, 771. (b) Ejima, A.; Terasawa, H.; Sugimori, M.; Tagawa, H. *J. Chem. Soc., Perkin Trans* 1 **1990**, 27. (c) Ejima, A.; Terasawa, H.; Sugimori, M.; Tagawa, H. *Tetrahedron Lett.* **1989**, *30*, 2639.
6. (a) Ciufolini, M., A.; Roschanger, F. *Angew. Chem., Int. Ed.* **1996**, *35*, 1692. (b) Henegar, K. E.; Ashford, S.; Baughman, T.A.; Sih, J.C.; Gu, R-L. *J. Org. Chem.* **1997,** *62*, 6588.
7. Curran, D. P.; Ko, S-.B.; Josien, H. *Angew. Chem., Int. Ed.* **1995**, *34*, 2683.
8. Jew, S-. S.; Ok, K. D.; Kim, H. J.; Kim, J. M.; Jeong, M. H.; Cho, Y-. S. *Tetrahedron Asymmetry* **1995**, *6,* 5683.
9. Fang, F. G.; Xie, S.; Lowery, M. W. *J. Org. Chem.* **1994**, *59*, 6142.
10. (a) Chavan, S. P.; Venkatraman, M. S. *Tetrahedron Lett.* **1998,** *39*, 6745. (b) Kraiss, G.; Povarny, T.; Schieber, P.; Nador, K. *Tetrahedron Lett*. **1973**, *14*, 4074.
11. Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed; VCH: New York, 1993.
12. Corey, E. J.; Ghosh, A. K. *Tetrahedon Lett.* **1988**, *29*, 3205.