Total Synthesis of (+)-Camptothecin via an Intramolecular Palladium-Catalyzed Cyclization Strategy

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Abstract: The novel cascade intramolecular Pd-catalyzed cyclization followed by aromatization for the construction of D ring of (+)-camptothecin as a key step is demonstrated.

Key words: natural products, alkaloids, antitumor, palladium, cyclizations



Figure 1 Camptothecin and its analogues.

The pentacyclic alkaloid camptothecin (CPT, 1), was isolated in 1966 by Wall and co-worker from Chinese tree *Camptotheca acuminata*.¹ Camptothecin and its

SYNLETT 2007, No. 17, pp 2635–2638 Advanced online publication: 25.09.2007 DOI: 10.1055/s-2007-991054; Art ID: G26507ST © Georg Thieme Verlag Stuttgart · New York analogues, collectively called camptothecins, which have been isolated from various botanical species viz. *Pyrenacantha klaineana*² and roots of *Ophiorrhiza pumila*,³ display promising anticancer activity. The structurally similar nothapodytine A (**4**) and B (**5**), recently isolated from *Nothapodytis foetida*,⁴ are the oxidised form of mappicine (**6**)⁵ and show antiviral activity, and foetidine **7** exhibits anti-HIV activity.⁶ Although camptothecin itself cannot be used as a drug because of its low solubility, toxic nature, and unstable lactone ring, two of its analogues, irinotecan (**2**) and topotecan (**3**), were launched as anticancer drugs and many others are in different stages of clinical trials (Figure 1).

To date numerous imaginative syntheses of **1** and its derivatives have been reported by various research groups;⁷ however, due to its low natural abundance, challenging structural features, unique mode of action (inhibition of DNA topoisomerase I), and promising biological activity, the chemical synthesis of camptothecins remains a challenge. Our group is also involved in the development of novel, simple, and practical routes toward camptothecins. We have developed various approaches towards camptothecin and mappicine ketone where the focus was on the construction of the D ring.⁸

As a result of our continuing interest in camptothecin and its analogues, we report herein a novel and efficient method for the construction of the D ring of camptothecin that employs cascade palladium-catalyzed oxidative cyclization followed by aromatization in one pot as the key step. The Wacker oxidation is a well-known reaction for the conversion of olefin into ketone employing PdCl₂ as a catalyst and CuCl, CuCl₂, *p*-benzoquinone, or H₂O₂ as a reoxidant.^{9,10}

A new synthetic approach towards 1, as depicted in Scheme 1, was undertaken where (+)-1 could be accessed from enol ether 28 by Sharpless asymmetric dihydroxylation followed by oxidation. The enol ether in turn could be obtained from diester 25 by selective reduction of the heteroaromatic ester. The diester 25 could be accessed from compound 23 by alkylation and carboxylation, compound 23 could be obtained from olefin 22 by Pd-catalyzed cascade cyclization followed by aromatization as a key step. Olefin 22 can be readily obtained from 21, which in turn could be readily prepared from keto compound 14 by Friedländer condensation, which in turn could be prepared from ethyl ester of glycine Schiff base 8.



Scheme 1 Retrosynthetic analysis

Accordingly, the synthesis began from simple Schiff base **8**, which was converted into allyl ketone **14** following a sequence of reactions as previously described by us (Scheme 2).^{8c} The keto compound **14** was protected as ketal to furnish protected compound **15** in 98% yield. With the compound **15** in hand, it was subjected to Wacker oxidation using PdCl₂ and CuCl₂ as a reoxidant in DMF-H₂O (3:1) at 95 °C, which resulted in the formation of the anticipated Wacker product **16** in 65% yield.¹⁰

After the successful Wacker oxidation on compound **15** (Scheme 2), we then decided to treat compound **17** under identical conditions (Scheme 3). The compound **17** was prepared from compound **15** by deprotection of CBz and further protection with ethyl malonyl chloride in 72%



Scheme 2 *Reagents and conditions*: (a) 10% NaOH (1.2 equiv), allyl bromide (1.2 equiv), TBAHSO₄ (0.1 equiv), CH₂Cl₂, r.t., 2 h, 96%; (b) 10% HCl (1.2 equiv), r.t., 0.5 h, 95%; (c) K₂CO₃ (1.2 equiv), benzylchloroformate (1.1 equiv), anhyd CH₂Cl₂, 0 °C, 1 h, 94%; (d) NaH (1.2 equiv), ethyl acrylate (1.2 equiv), C₆H₆, r.t., 1 h, refluxed 2–3 h; (e) NaCl (4.0 equiv), DMSO–H₂O (3:1), 120–130 °C, 6 h, 68%; (f) ethylene glycol (1.2 equiv), PTSA (cat.), anhyd C₆H₆, reflux, 6 h, 98%; (g) PdCl₂ (0.1 equiv), CuCl₂ (2.1 equiv), O₂, DMF–H₂O (3:1), 95 °C, 8 h, 65%.

the Wacker oxidation conditions identical to those of **15**.¹⁰ Surprisingly, instead of the expected Wacker product viz. ketone 18, it resulted in the formation of a mixture of cyclized product 19 in 38% yield along with 20 in 43% yield. Performing this reaction under N₂ atmosphere gave the same result. This indicated that there is no role for O_2 , and the ketone 18 could not be detected as an intermediate. This result can be rationalized by invoking the complexation of Pd with the olefin followed by attack of the malonate carbon as an internal nucleophile, even in the presence of water nucleophile (Wacker oxidation); after the β -H elimination, the Pd catalyst is regenerated and isomerization into internal double bond results in the formation of 19. A competing elimination of H results in the formation of isomeric olefin 20. The compound 19 is a key intermediate in Shamma's approach for camptothecin.¹¹ It is pertinent to mention that earlier Hegedus¹² and co-workers have observed Pd (II)-catalyzed intermolecular alkylation of olefins, and very recently Widenhoefer et al. have also observed a similar intramolecular cyclization where 1,3-diketo and β -keto ester olefins were used as the substrate in the presence of PdCl₂(MeCN)₂ as the catalyst under different reaction conditions.¹³

yield after two steps. The compound 17 was subjected to



Scheme 3 Reagents and conditions: (a) KOH (14.0 equiv), EtOH, reflux, 6–8 h; (b) K_2CO_3 (1.2 equiv), ethyl malonyl chloride (1.2 equiv), anhyd CH₂Cl₂, 0 °C, 1 h, 72% over two steps; (c) PdCl₂ (0.1 equiv), CuCl₂ (2.1 equiv), DMF–H₂O (3:1), 95 °C, 7 h, 81% (38% **19** + 43% **20**).

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Scheme 4 *Reagents and conditions*: (a) *N*-(*o*-aminobenzilidine)-*p*-toluidine (1.2 equiv), PTSA (cat.), anhyd toluene, azeotropic distillation 3–4 h, 75%; (b) KOH (14.0 equiv), EtOH, reflux, 8 h; (c) K_2CO_3 (1.2 equiv), ethyl malonyl chloride (1.2 equiv), anhyd CH_2Cl_2 , 0 °C, 1 h, 71% in two steps; (d) PdCl₂ (0.1 equiv), CuCl₂ (2.1 equiv), DMF–H₂O (3:1), 95 °C, 6 h, 54%; (e) LDA (1.1 equiv), diethyl carbonate (1.0 equiv), THF, -78 °C, 3–4 h, 70%; (f) NaH (1.1 equiv), EtI (1.1 equiv), anhyd DME, 0 °C to r.t., 3–4 h, 64%; (g) DIBAL-H (3.0 equiv), anhyd THF, -60 °C, 2 h, 83%; (h) NaBH₄ (2.0 equiv), THF–H₂O (5:1), 0 °C, 0.5 h, 90%; (i) MsCl (4.0 equiv), Et₃N (8.0 equiv), anhyd THF, r.t., 24 h, 92%; (j) (DHQD)₂-py (cat.), OsO₄ (cat.), K₃Fe(CN)₆ (3.0 equiv), K₂CO₃ (3.0 equiv), MeSO₂NH₂ (1.0 equiv), *t*-BuOH–H₂O (1:1), 0 °C, 7 h; (k) I₂ (12.5 equiv), CaCO₃ (12.5 equiv), MeOH–H₂O (2:1), r.t., 24 h, 33% in two steps.

By taking advantage of the result obtained (Scheme 3), we decided to exploit this result for the synthesis of (+)-1 by employing this methodology on tricyclic compound 22. The olefin keto ester was synthesized from keto compound 14, as depicted in Scheme 4, following our previously established conditions.^{8c} Accordingly, when compound 22 was subjected to Wacker conditions,¹⁰ we unexpectedly observed formation of aromatized product 23 (54%) as the sole product. This may be ascribed to airoxidation of the initially formed tetracyclic dihydro compound under the driving force of aromatization. A noteworthy feature of this transformation is the Pd-catalyzed oxidative cyclization followed by concomitant aromatization in one pot.¹⁴ Having secured the tetracyclic rings of the pentacyclic camptothecin, the last ring (E) was achieved as follows. The tetracyclic compound 23 was further treated with diethyl carbonate using LDA as the base to furnish compound 24 in 70% yield.¹⁵ Compound 24 was alkylated with ethyl iodide using sodium hydride as the base, furnishing compound 25 in 64% yield.¹⁶ This compound 25 is the same intermediate as described in our earlier synthesis of camptothecin.^{8a} The diester 25 was converted into (+)-camptothecin (1) as previously described.8e

Selective reduction of heteroaromatic ester to aldehyde was accomplished using 3 equivalents DIBAL-H in THF at -60 °C and furnished aldehyde **26** in very good yield (83%). Aldehyde **26** was subjected to 2 equivalents sodium borohydride in a mixture of solvent (THF–H₂O, 5:1) at 0 °C provided lactol **27** in excellent yield (90%). The lactol **27** was transformed into enol ether **28** in excellent

yield (92%) via O-mesylation followed by elimination.^{8e} It is pertinent to mention that the asymmetric dihydroxylation followed by oxidation have also been employed on DE ring and CDE rings to install the one chiral center of camptothecin,¹⁷ which leads to solubility problems at early stage and leads to waste of expensive chiral substrate in subsequent transformations. Since the molecule contains only one chiral center, it makes sense to introduce the chirality at a late stage or at the end of the synthesis, thereby addressing the solubility issues and the loss of chiral substrate, and thus maintain chiral economy. Accordingly, we decided to do the Sharpless AD at the last step and thus, Sharpless asymmetric dihydroxylation followed by oxidation was readily converted into (+)-camptothecin (1), the rotation is $[\alpha]_D^{25}$ +39 (*c* 0.142, CHCl₃–MeOH, 4:1), lit. +45, (*c* 0.30 CHCl₃–MeOH, 4:1) which was described by us earlier^{8e} or most recently by improved procedure accomplished by Yao et al.¹⁸ The spectroscopic data of synthetic (+)-1 was in complete agreement with those of the natural compound.

In summary, we have demonstrated a novel and efficient Pd-catalyzed oxidative cyclization and aromatization cascade reaction in one pot for the construction of D ring of camptothecin and its analogues. Thus we have achieved the total synthesis of (+)-camptothecin (1) in sixteen steps in 1.5% overall yield.

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(14) Synthesis of Compound 23: Procedure for the Pd-Catalyzed Cyclization Reaction

To a stirred solution of compound **22** (0.2 g, 0.61 mmol) in DMF (3.0 mL) and H₂O (1.0 mL) was added PdCl₂ (0.007 g, 0.061 mmol) and CuCl₂·2H₂O (0.22 g, 1.2 mmol). The resultant dark green solution was heated at 95 °C for 8 h. After the disappearance of starting material (TLC), the reaction mixture was cooled to r.t. Then, H₂O (10 mL) was added and extracted with Et₂O (3×15 mL). The combined organic layers were washed with H₂O (3×10 mL), brine (10 mL), dried over anhyd Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO₂) using EtOAc–PE (6:4) as an eluent to furnish cyclized product **23** as a pale yellow solid in 54% yield, mp 97–100 °C.

Spectroscopic Data for Compound 23

IR (CHCl₃): $v_{max} = 1728$, 165 \overline{s} , 1604 cm⁻¹. ¹H NMR (400 MHz, CDCl₃ and CCl₄): $\delta = 1.44$ (3 H, t, J = 7.2 Hz), 2.46 (3 H, s), 4.46 (2 H, q, J = 7.2 Hz), 5.27 (2 H, s), 7.21 (1 H, s), 7.66 (1 H, t, J = 8.0 Hz), 7.82 (1 H, t, J = 8.0 Hz), 7.92 (1 H, d, J = 8.0 Hz), 8.22 (1 H, d, J = 8.0 Hz), 8.37 (1 H, s) ppm. ¹³C NMR (100 MHz, CDCl₃ and CCl₄): $\delta = 14.3$, 20.4, 50.15, 61.5, 103.5, 124.0, 127.95, 128.1, 129.1, 129.8, 130.5, 131.0, 136.0, 145.7, 148.9, 151.0, 152.4, 158.4, 166.3 ppm. ESI-MS: m/z = 321 [M + H]⁺, 343 [M + Na]⁺. Anal. Calcd (%) for C₁₉H₁₆N₂O₃: C, 71.24; H, 5.03; N, 8.74. Found: C, 71.19; H, 5.11; N, 8.69.

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