DOI: 10.1002/asia.201000073

Efficient Total Synthesis of (*S*)-14-Azacamptothecin

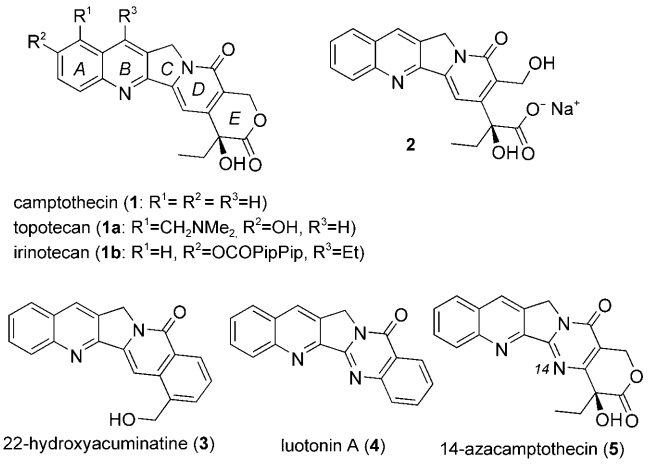
Guan-Sai Liu,[a, b] Yuan-Shan Yao,[a, b] Peng Xu,[a, b] Shaozhong Wang,[a] and Zhu-Jun Yao*[a, b]

Abstract: An efficient total synthesis of (*S*)-14-azacamptothecin has been accomplished in 10 steps and 56% overall yield from 5*H*-pyrano[4,3-d]pyrimidine **8**. A mild Hendrickson reagent-triggered intramolecular cascade cyclization, a highly enantioselective dihydroxylation, and an efficient palladium-catalyzed transformation of an *O*-allyl into *N*-allyl group are the key steps in the synthesis. This work provides a much higher overall yield than the previous achievement and shows sound flexibility for the further applications that will lead to new bioactive analogues.

Keywords: 14-azacamptothecin · allyl migration · asymmetric dihydroxylation · cyclization · total synthesis

Introduction

Camptothecin (CPT, **1**) is a representative of the unique pentacyclic alkaloids isolated from Chinese medicinal plant *Camptotheca acumunata*.[1] The potent anticancer activities and unusual action mechanisms by inhibiting DNA topoisomerase I[2] have made CPT an excellent and successful lead for drug discovery and development in the past several decades.[3] Other natural alkaloids in this family, including 22-hydroxyacuminatine (**3**)[4] and luotonin A (**4**),[5] have also been found to display similar inhibitory properties against DNA Top I. Unfortunately, camptothecin itself could not be used in clinical treatments because of its poor water solubility and high toxicity. Initial clinical trials of CPT in the early 1970s were administered with its more toxic and less potent sodium salt **2**. Continuous endeavors in the medicinal chemistry of CPT in the past decades have made great successes. The semi-synthetic, more water-soluble analogues topotecan (**1a**) and irinotecan (**1b**) have now been successfully applied in the clinical treatments of a number of cancers.[6,7] Several additional CPT analogues have also been developed and studied in different stages of clinical trials.[8]14-Azacamptothecin (**5**) is one of the water-soluble CPT analogues recently developed by Hecht and co-workers,[9] in which the C-14 carbon atom of natural camptothecin (**1**) is replaced with a nitrogen atom. It was firstly synthesized by utilizing a radical cyclization strategy by the same group.[10] Such aza modification greatly improves the water solubility of the compound and thus facilitates the corresponding biomedical research. Furthermore, evidence has shown that 14-azacamptothecin can stabilize the topoisomerase I-DNA complex at the same sites as CPT with a



[a] G.-S. Liu, Y.-S. Yao, P. Xu, Dr. S. Wang, Prof. Dr. Z.-J. Yao
Nanjing National Laboratory of Microstructures
School of Chemistry and Chemical Engineering
Nanjing University
22 Hankou Road, Nanjing, Jiangsu 210093 (China)
E-mail: yaoz@sioc.ac.cn
yaoz@nju.edu.cn

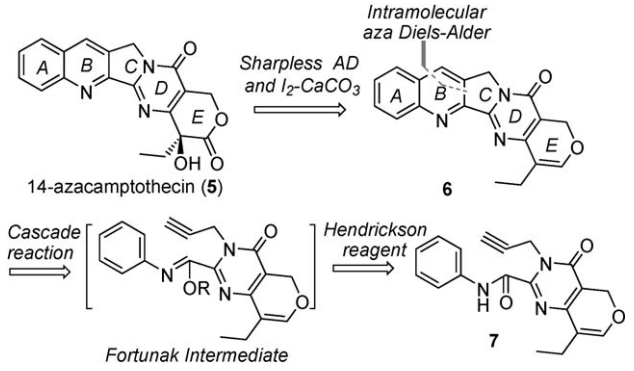
[b] G.-S. Liu, Y.-S. Yao, P. Xu, Prof. Dr. Z.-J. Yao
Joint Laboratory of Green Chemistry
Department of Chemistry
University of Science and Technology of China
Hefei, Anhui 230026 (China)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.201000073.

somewhat more potent IC_{50} value.[9] Therefore, 14-azacamptothecin shows great potential as a new lead structure for the future design and development of anticancer drugs.

For a significant difference from the basic skeleton of camptothecin, total synthesis is now the only entrance to acquire the samples of 14-azacamptothecin[10] and other related derivatives.[11] However, the relatively low overall yield (0.6% yield in 10 total steps) and the inefficient radical cyclization (28% yield in a single step) in the previously achieved total synthesis of 14-azacamptothecin[10] encumber the progress of further applications. In the synthesis of another derivative, 10,11-methylenedioxy-14-azacamptothecin, a much lower yield (6%) has been achieved in the key radical cyclization.[11] Undoubtedly, the development of a more efficient total synthesis of 14-azacamptothecin would be helpful in acquiring more clinically useful derivatives of 14-azacamptothecin. Prompted by our recent achievements in the total syntheses of camptothecin (**1**), luotonin A (**4**), and 22-hydroxyacuminatine (**3**) by using an efficient Hendrickson reagent-triggered mild cascade reaction,[12–14] we attempted to extend our methodology to the synthesis of 14-azacamptothecin. Herein, we wish to report our recent results in the total synthesis of (*S*)-14-azacamptothecin (**5**) by utilizing the mild cascade methodology, and our exploration in the enantioselective dihydroxylation of multiple nitrogen-containing cyclic enol ethers.

The formation of the α-hydroxyl lactone moiety of 14-azacamptothecin was devised in the final stages of the total synthesis in our initial retrosynthesis (Scheme 1). Sharpless asymmetric dihydroxylation (Sharpless AD) of the cyclic enol ether **6** and subsequent iodine-mediated oxidation of the resulting hemiacetal intermediate were employed to establish the lactone moiety and its C-20 stereochemistry. Our recently developed aza Diels–Alder approach[14] via the Fortunak intermediate[15] was considered to construct both the B and C rings of key cyclic enol ether **6** from the simple amide **7** in a one-pot fashion.



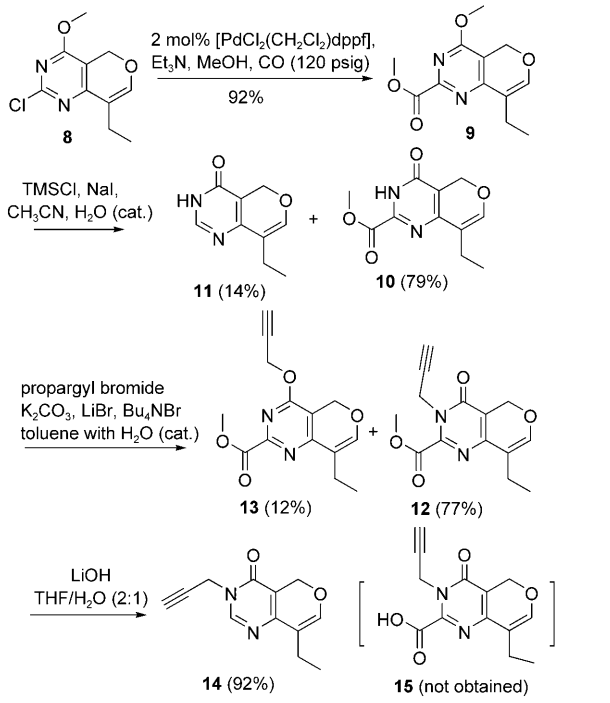
Scheme 1. Initial retrosynthesis of 14-azacamptothecin (**5**).

Abstract in Chinese:

本文报道了一条高效率的十步全合成(*S*)-14-氮杂喜树碱的新路线，总收率达到 56%；其中 Hendrickson 试剂引发的串联成环法，环状烯醇醚的对映选择性双羟基化以及钯催化的 *O*-烯丙基向 *N*-烯丙基的转化作为关键方法被成功应用。与以前的报道结果相比，本工作在总产率上有显著的提高，并且体现了较好的结构可变性，有利于进一步发展具有生理活性的结构类似物。

Results and Discussion

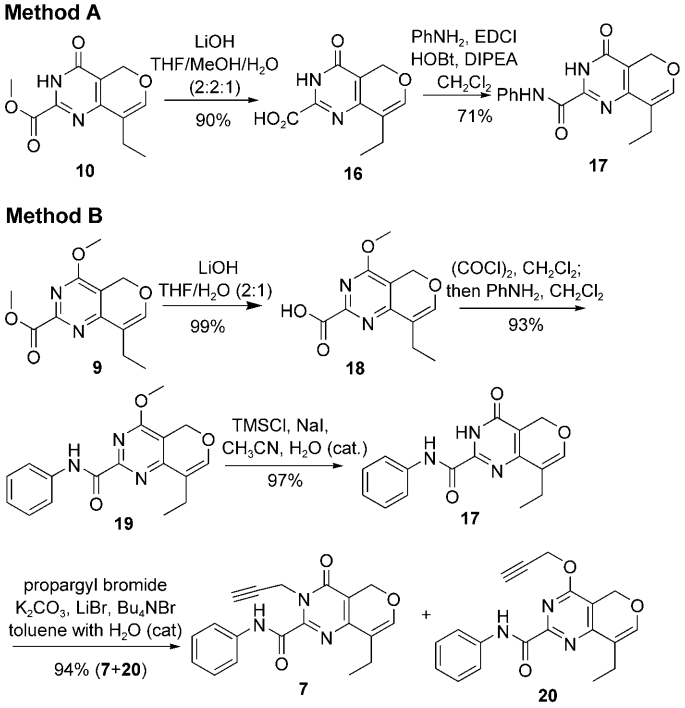
Synthesis of the stable amide 7: Following the above retrosynthesis (Scheme 1), the chemically stable amide **7** was synthesized at first. Chloropyrimidine **8**, a known common intermediate in the previous syntheses of 14-azacamptothecin[10] and 10,11-methylenedioxy-14-azacamptothecin,[11] was utilized in this work again (Scheme 2). Catalytic carbonylation of chloropyrimidine **8** was smoothly accomplished under a CO atmosphere (120 psig) in the presence of 2 mol% of $[PdCl_2(CH_2Cl_2)(dppf)]$ (dppf = 1,1′-bis(diphenylphosphino)ferrocene) and Et_3N in methanol at 90 °C affording the corresponding methyl ester **9** (92%). O-Demethylation of **9** with trimethylsilyl chloride (TMSCl) and sodium iodide[16] in acetonitrile and a catalytic amount of water gave pyrimidinone **10** (79%) and another minor decarboxylation byproduct **11** (14%). Treatment of **10** with propargyl bromide, K_2CO_3, and LiBr in the presence of a catalytic amount of tetrabutylammonium bromide in toluene[17] provided N-propargylation product **12** (77%) and O-propargylation product **13** (12%), respectively. Unfortunately, further hydrolysis of methyl ester **12** with LiOH did not afford the



Scheme 2. Attempts to synthesize carboxylic acid **15**. DIEPA = diisopropylethylamine.

expected carboxylic acid **15**. Instead, a decarboxylation product **14** (92%) was provided.

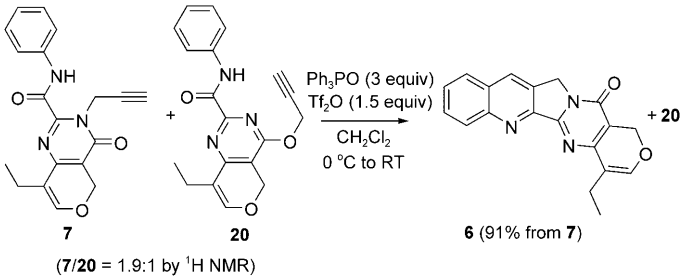
To avoid the undesired decarboxylation, two protocols, slightly altering the reaction order, were explored (Scheme 3). In method A, basic hydrolysis of the methyl



Scheme 3. Synthesis of amides **17** and **7**.

ester **10** with LiOH in THF/MeOH/H_2O 2:2:1 at room temperature gave the acid **16** (90%). To our delight, the decarboxylation was not detected in this case. Further treatment of **16** with aniline in the presence of *N*′-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide (EDCI) and 1-hydroxybenzotriazole (HOBt) in dichloromethane at room temperature afforded the corresponding amide **17** (71%). In another parallel method, B, basic hydrolysis of the methyl ester **9** gave the corresponding carboxylic acid **18** in 99% yield. Conversion of acid **18** to its corresponding acid chloride followed by treatment with aniline afforded amide **19** (93%). O-Demethylation of **19** was then carried out with TMSCl and sodium iodide[16] in acetonitrile, giving the corresponding amide **17** (97%). Relatively, method B (89% yield from **9**) is more efficient than A (50% yield from **9**) for the synthesis of amide **17**. Unfortunately, further N-propargylation by treatment of amide **17** with propargyl bromide provided an inseparable mixture of the desired product **7** and the byproduct **20** (**7**/**20** 1.9:1, determined by ^{1}H NMR spectroscopy) in a combined yield of 94%.

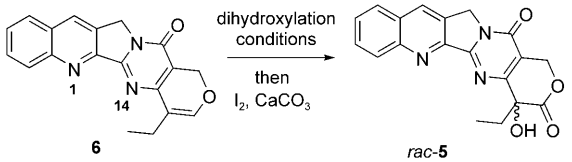
Synthesis of pentacyclic precursor 6: Because the byproduct **20** (Scheme 3) is inert under the subsequent reaction conditions, the mixture of **7** and **20** was directly used for the next step. Treatment of this mixture with freshly prepared Hendrickson reagent (bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate) for 30 min at 0°C to room temperature afforded the needed cyclic enol ether **6** (56% overall yield from amide **17**, Scheme 4) and the unreacted **20** after separation by silica-gel flash chromatography. The corrected yield of converting **7** to **6** is 91% with consideration of the ratio of reactants.



Scheme 4. Cascade synthesis of pentacyclic precursor **6**.

Oxidations of cyclic enol ethers: With the entire pentacyclic skeleton **6** in hand, oxidations towards the final target **5** were then attempted. Sharpless dihydroxylation was designed as a crucial step to establish the stereochemistry of 14-azacamptothecin (**5**) in this synthesis (Scheme 1).[14a,16,18–19] Treatment of the enol ether **6** with the standard Sharpless asymmetric dihydroxylation conditions (K_2OsO_4, $K_3[Fe(CN)_6]$, K_2CO_3, hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether ($(DHQD)_2$-PYR), $MeSO_2NH_2$, *t*BuOH/H_2O, 0°C, 24 h)[20] and followed by further treatment with iodine and $CaCO_3$ afforded a satisfactory yield of lactone **5**. To our surprise, chiral HPLC analysis of the obtained sample **5** indicated that it was completely racemic (Table 1, entry 1). The use of another commonly used chiral ligand, $(DHQD)_2$-PHAL, also provided the negative results (entry 2). Additional optimizations of reaction conditions all failed, including altering the solvents and temperatures and

Table 1. Dihydroxylations of the pentacyclic intermediate **6**.

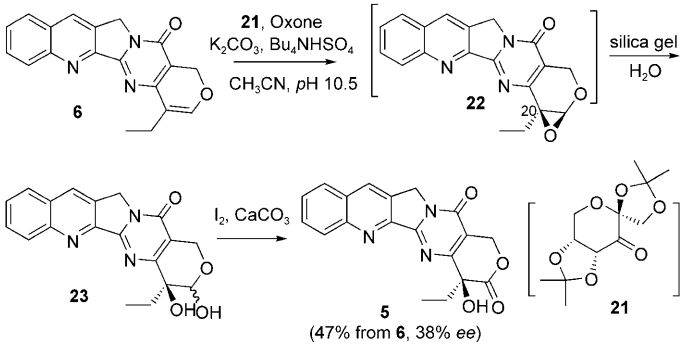


Entry	Conditions	Yield [%][a]	*ee* [%][b]
1	K_2OsO_4, $K_3[Fe(CN)_6]$, K_2CO_3, $(DHQD)_2PYR$, $MeSO_2NH_2$, *t*BuOH, H_2O, 0°C, 24 h	65	0
2	K_2OsO_4, $K_3[Fe(CN)_6]$, K_2CO_3, $(DHQD)_2PHAL$, $MeSO_2NH_2$, *t*BuOH, H_2O, 0°C, 24 h	68	0
3	K_2OsO_4, NMO, THF, H_2O	85	0

[a] The overall isolated yields of *rac*-**5**. [b] Determined by chiral HPLC. NMO = *N*-methylmorpholine-*N*-oxide.

the use of different amounts of the catalyst and ligand. More interestingly, the ligand-free conditions gave the highest yield of *rac*-**5** (85%, entry 3).

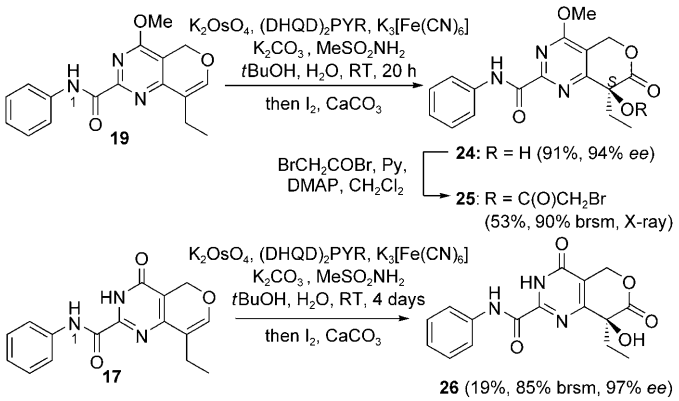
Failure in the enantioselective dihydroxylations suggested to us that certain structural factors in substrate **6** prevented the Sharpless AD from achieving satisfactory enantioselectivity. Comparison with similar substrates in previous successful syntheses of camptothecin[14a,18–19] indicated that the two spatially-close nitrogen atoms (N-14 and N-1, see Table 1) in the cyclic enol ether **6** might disrupt the effective coordination of osmium with the chiral ligand during the AD reactions.[20] To overcome the above drawback, two alternatives could be considered in introducing the required oxygenated stereogenic center. One is to apply metal-free oxidations upon the cyclic enol ether **6** and the other is to use ligand-ability-free olefin precursors as the substrate of Sharpless AD. Since the enol ether **6** was available, we firstly examined Shi's asymmetric epoxidation (Scheme 5).



Scheme 5. Shi's epoxidation of cyclic enol ether **6** and subsequent transfomations to **5**.

Treatment of **6** with Shi's epoxidation conditions[21] by using a catalytic amount of ketone **21** afforded an unstable epoxide **22**, which was immediately converted to the diol **23** with water in the presence of silica gel. Further oxidation of **23** with iodine and $CaCO_3$ provided 14-azacamptothecin (**5**) in 47% overall yield in 3 steps from **6**. Unfortunately, the optical purity of this product was again unsatisfactory (38% *ee* (*ee* = enantiomeric excess) as measured by chiral HPLC analysis). Further efforts in optimizing the reaction temperatures, solvents, amounts of catalyst **21**, and pH of reaction media could not improve the enantioselectivity.

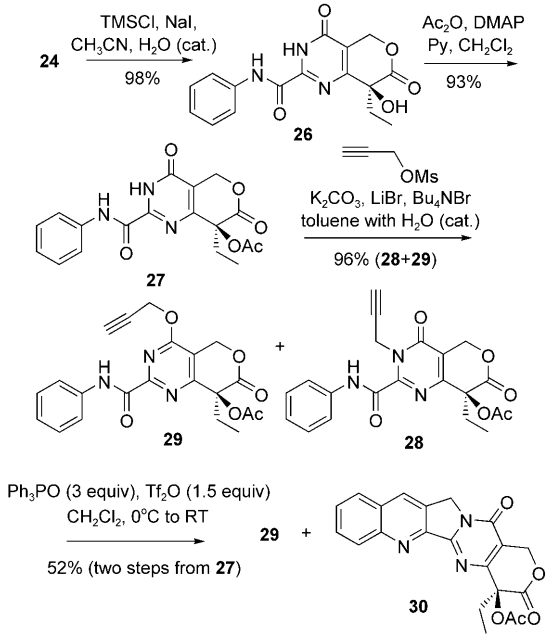
Because both Sharpless dihydroxylation and Shi epoxidation could not achieve satisfactory enantioselectivities when using the cyclic enol ether **6** as the oxidation substrate, two early-stage cyclic enol ethers **17** and **19** (Scheme 3) were then taken into our consideration. In both amide compounds, their N-1 atom lacks strong coordinating ability with osmium in the Sharpless dihydroxylations. To our delight, treatment of enol ether **19** with previously used Sharpless AD conditions followed by further oxidation with I_2 and $CaCO_3$ successfully afforded the required lactone **24** in 91% yield and with 94% *ee* (determined by HPLC analysis, see the Supporting Information) (Scheme 6). Its *S* configuration was further confirmed by an X-ray single-crystal analysis of the bromoacetate **25** (see the Supporting Information).



Scheme 6. Dihydroxylation of enol ethers **19** and **17**.

However, the parallel reaction of **17** was quite slow and gave only a 19% yield of **26** (97% *ee* determined by HPLC) after four days, along with a substantial amount of starting material **17**. The use of larger amounts of chiral ligand and K_2OsO_4 could not improve the results in the later case.

N-Propargylation and cascade cyclization: Treatment of α-hydroxylactone **24** with TMSCl and sodium iodide[16] in acetonitrile afforded the amide **26** in 98% yield (Scheme 7). Because of its poor solubility in many regular organic solvents, tertiary alcohol **26** was then converted to the more soluble acetate **27** (93%) by using acetic anhydride, pyri-

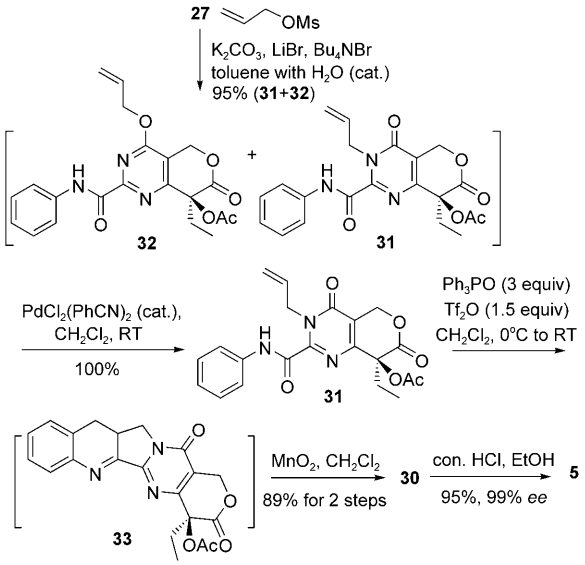


Scheme 7. N-Propargylation and the subsequent cascade cyclization.

dine, and a catalytic amount of 4-dimethylaminopyridine (DMAP) in dichloromethane. Again, propargylation of **27** with prop-2-ynyl methanesulfonate provided an inseparable mixture of N-propargylation product **28** and O-propargylation byproduct **29** in 96% yield (ratio 1.5:1 as measured by ^{1}H NMR spectroscopy), and no N-propargylation product on the aniline amide nitrogen atom was observed. All attempts failed to improve the ratio between the required compound **28** and the byproduct **29** by optimizing reaction temperatures, solvents, and bases.

Although poor selectivity of N- and O-propargylation was achieved, exploration of the subsequent intramolecular cyclization continued. The above mixture of **28** and **29** was immediately treated with bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate at 0°C and at room temperature for 2 h. The desired pentacyclic product **30** was obtained in 52% yield (from **27**) after purification by silica-gel column chromatography. By adjustment of the reactants ratio of **28** and **29** (1.5:1), the actual yield of this cascade reaction (from **28** to **30**) was approximately 90%.

Pd-catalyzed allyl transformation and completion of the total synthesis: As mentioned above, poor selectivities of N- and O-alkylations (**12**/**13** 6.4:1 in Scheme 2, **7**/**20** 1.9:1 in Scheme 3, **28**/**29** 1.5:1 in Scheme 7) were often given under the previous propargylation conditions. Although our work was very close to the target **5**, further improvement on the N-alkylation selectivity was needed for a satisfactory synthesis. An internal transformation of the *O*-allyl derivative to the corresponding *N*-allyl derivative was considered by using the palladium-catalyzed conditions.[22,23] Since uncertain allenic intermediates might be produced in the reaction of *O*-propargyl derivative **29**, rearrangement of an alternative *O*-allyl compound **32** to the *N*-allyl compound **31** was examined (Scheme 8).



Scheme 8. Pd-catalyzed allyl transformation and completion of the total synthesis.

Reaction of **27** with allyl methanesulfonate provided an inseparable mixture of **31** and **32** (ratio 1.35:1 as measured by ^{1}H NMR spectroscopy) in 95% combined yield.[17] Treatment of this mixture with $[PdCl_2(PhCN)_2]$ (5 mol%) in CH_2Cl_2 for 2 h at RT afforded the *N*-allyl product **31** in a quantitative yield. Obviously, treatment with simple allylation conditions followed by Pd-catalyzed *O*-allyl migration provides a new high-yield entrance to the sole *N*-allyl 2-pyridone derivatives, which have been frequently involved as the key intermediates in the syntheses of many camptothecin-family alkaloids.[3e] Treatment of **31** with bis(triphenyl)-oxodiphosphonium trifluoromethanesulfonate at 0°C and room temperature[24] followed by oxidation with freshly prepared MnO_2 provided (*S*)-**30** in 89% yield. Final deacetylation of **30** was carried out with concentrated HCl in ethanol, providing (*S*)-14-azacamptothecin (**5**, 95%, >99% *ee* by HPLC analysis).

Conclusions

A new enantioselective total synthesis of (*S*)-14-azacamptothecin has been accomplished from a known 5*H*-pyrano[4,3-d]pyrimidine intermediate. A mild Hendrickson reagent-triggered cascade cyclization, an efficient Pd-catalyzed transformation of *O*-allyl to *N*-allyl, and a highly enantioselective dihydroxylation successfully served as the key steps in the synthesis. Relative to the previous achievement, this work (10 steps, 56% yield from **8**) presents a much higher overall yield and shows sound flexibility for further applications that may lead to new bioactive analogues with pharmaceutical interests.

Experimental Section

General: Unless stated otherwise, all reactions were carried out in dried glassware under a dry nitrogen atmosphere. All melting points were uncorrected. All solvents were purified and dried prior to use. Optical rotations were measured at the sodium D line (589 nm) with a 1.00 dm path length cell. IR spectra were recorded on an FT-IR instrument. ^{1}H NMR spectra were recorded at 300 MHz, and ^{13}C NMR spectra were recorded at 75 MHz, and assigned in parts per million (δ). Reference peaks for chloroform in ^{1}H NMR and ^{13}C NMR spectra were set at 7.27 ppm and 77.0 ppm, respectively. For [D$_6$]DMSO, the reference peaks in ^{1}H NMR and ^{13}C NMR spectra were set at 2.50 ppm and 40.0 ppm, respectively. Flash column chromatographies were performed on silica gel H (10–40 μ).

Methyl 8-ethyl-4-methoxy-5*H*-pyrano[4,3-d]pyrimidine-2-carboxylate (9): An autoclave vessel containing **8** (2.69 g, 11.9 mmol), $[PdCl_2(CH_2Cl_2)(dppf)]$ (0.19 g, 0.24 mmol, 2 mol%), Et_3N (4.15 mL, 29.7 mmol), and CH_3OH (50 mL) was purged with nitrogen and then with carbon monoxide (120 psig) and heated to 90°C. The reaction mixture was vigorously stirred for 5 h, and then allowed to cool down to room temperature and vented. The solids were removed by filtration through a pad of Celite and washed with EtOAc (100 mL). The filtrate and washings were combined and concentrated. The residue was purified by silica-gel flash chromatography (CH_2Cl_2) to afford **9** (2.74 g, 92%) as a white solid. M.p. 114–116°C; IR (KBr): $\tilde{\nu}$ = 3012, 2987, 2964, 2512, 1745, 1639, 1575, 1550, 1475, 1464, 1446, 1397, 1368, 1256, 1205, 1134, 1063, 968, 937, 827, 759 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.74 (1H, s), 5.16 (2H, s), 4.07 (3H, s), 4.00 (3H, s), 2.49 (2H, q, J = 7.5 Hz), 1.15 ppm (3H, t, J =

7.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 164.4, 164.3, 158.4, 155.4, 149.9, 117.4, 107.1, 62.4, 54.1, 53.0, 19.2, 13.2 ppm; MS (ESI): *m*/*z*: 251 $[M+H]^+$; elemental analysis calcd (%) for $C_{12}H_{14}N_2O_4 \cdot 0.2H_2O$: C 56.78, H 5.72, N 11.04; found: C 56.67, H 5.56, N 11.19.

8-Ethyl-4-methoxy-5*H*-pyrano[4,3-d]pyrimidine-2-carboxylic acid (18): lithium hydroxide monohydrate (0.38 g, 9 mol) was added to a solution of ester **9** (1.50 g, 6 mmol) in THF (20 mL) and water (10 mL) at 0 °C. After the reaction had been stirred at the same temperature for 30 min, the whole mixture was concentrated in vacuo and the residue was re-dissolved into water (10 mL). The pH was adjusted to 4–5 by the addition of 1 N HCl. The resultant precipitation was collected by filtration and dried, giving **18** (1.40 g, 99 %) as a white solid. M.p. 137–139 °C; IR (KBr): $\tilde{\nu}$ = 3469, 2968, 1709, 1574, 1375, 1240, 1071, 941, 729 cm^{-1}; ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 13.40 (1H, s), 7.00 (1H, s), 5.15 (2H, s), 3.97 (3H, s), 2.40–2.33 (2H, m), 1.07 ppm (3H, t, *J* = 7.5 Hz); ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 165.2, 164.2, 157.9, 156.8, 151.0, 116.8, 106.6, 62.3, 54.5, 19.2, 14.0 ppm; MS (ESI): *m*/*z*: 235 $[M-H]^-$; elemental analysis calcd (%) for $C_{11}H_{12}N_2O_4$: C 55.93, H 5.12, N 11.86; found: C 56.07, H 5.14, N 11.89.

8-Ethyl-4-methoxy-*N*-phenyl-5*H*-pyrano[4,3-d]pyrimidine-2-carboxamide (19): The acid **18** (0.83 g, 3.51 mmol) in CH_2Cl_2 (18 mL) was treated with $(COCl)_2$ (0.92 mL, 10.52 mmol) and catalytic amount of DMF at 0 °C. After gas evolution ceased, the reaction mixture was concentrated and dried in vacuo. The residue was redissolved in CH_2Cl_2 (10 mL) and introduced into a suspension of aniline (0.32 mL, 3.51 mmol) and $NaHCO_3$ (0.88 g, 10.52 mmol) in CH_2Cl_2 (8 mL). After 2 h, water was added to the reaction mixture. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Purification by silica-gel flash chromatography (EtOAc/hexane 1:6) gave **19** (1.01 g, 93 %) as a white solid. M.p. 134–136 °C; IR (KBr): $\tilde{\nu}$ = 3419, 2360, 1637, 1533, 1385, 1130, 750, 617 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.95 (1H, s), 7.80–7.77 (2H, m), 7.44–7.39 (2H, m), 7.20–7.15 (1H, m), 6.80 (1H, t, *J* = 1.2 Hz), 5.22 (2H, s), 4.17 (3H, s), 2.54 (2H, dq, *J* = 7.5, 1.2 Hz), 1.24 ppm (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 165.0, 159.9, 157.5, 156.2, 150.3, 137.5, 129.0, 124.4, 119.5, 116.7, 106.6, 62.5, 54.3, 19.4, 13.4 ppm; MS (ESI): *m*/*z*: 334 $[M+Na]^+$; elemental analysis calcd (%) for $C_{17}H_{17}N_3O_3$: C 65.58, H 5.50, N 13.50; found: C 65.54, H 5.37, N 13.48.

(*S*)-8-Ethyl-8-hydroxy-4-methoxy-7-oxo-*N*-phenyl-7,8-dihydro-5*H*-pyrano[4,3-d]pyrimidine-2-carboxamide (24): A mixture of $(DHQD)_2$-PYR (14 mg, 0.016 mmol, 5 mol %), $K_3[Fe(CN)_6]$ (317 mg, 0.96 mmol), K_2CO_3 (133 mg, 0.96 mmol), $K_2[OsO_2(OH)_4]$ (1.18 mg, 3.21 μmol, 1.0 mol %), and $CH_3SO_2NH_2$ (61 mg, 0.64 mmol) in water (1.5 mL) and *tert*-butanol (1.5 mL) was stirred at room temperature until both phases were clear. The mixture was then cooled down to 0 °C, and enol ether **19** (100 mg, 0.32 mmol) was added in one portion. The reaction was allowed to warm to RT and was stirred for 20 h. The reaction was quenched at the same temperature by adding sodium sulfite (0.5 g), and stirred for an additional 30 min. The aqueous layer was extracted with a mixture of CH_2Cl_2 and CH_3OH (10 mL × 2, 10:1). The combined organic layers were dried over Na_2SO_4 and concentrated.

Crystalline iodine (1.22 g, 4.8 mmol, 15 equiv) and $CaCO_3$ (160 mg, 1.6 mmol, 5 equiv) were added to the above residue in a mixture of CH_3OH and H_2O (15 mL, 2:1). The whole mixture was stirred at 40 °C for 15 h. Na_2SO_3 (1.3 g) was then added slowly. CH_3OH was removed under reduced pressure, and then CH_2Cl_2 (10 mL), CH_3OH (1 mL), and H_2O (10 mL) were added. The aqueous layer was extracted with a mixture of CH_2Cl_2 and CH_3OH (10:1, 10 mL × 2). The combined organic layers were dried over Na_2SO_4 and concentrated. Purification by flash column chromatography on silica gel (CH_2Cl_2/CH_3OH 60:1) afforded **24** (100 mg, 91 %) in 94 % *ee* (HPLC conditions: Chiralcel AD-H column (0.46 × 15 cm), *n*-hexane/*i*PrOH 80:20 as mobile phase, flow rate: 1 mL min^{-1}, UV detection at 254 nm; t_R ((*S*)-isomer): 19.9, t_R ((*R*)-isomer): 30.4 min). M.p. 147–149 °C; $[\alpha]_D^{19}$ = 44 (*c* = 1.0 in $CHCl_3$/CH_3OH 3:1); IR (KBr): $\tilde{\nu}$ = 3440, 2978, 1751, 1603, 1542, 1373, 1155, 1037, 874, 761 cm^{-1}; ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 10.67 (1H, s), 7.82 (2H, dd, *J* = 8.7, 0.9 Hz), 7.45–7.40 (2H, m), 7.20–7.15 (1H, m), 6.38 (1H, s), 5.53 (1H, AB, *J* = 16.2 Hz), 5.44 (1H, AB, *J* = 16.2 Hz), 4.14 (3H, s), 2.01–1.87 (2H, m), 0.84 ppm (3H, t, *J* = 7.4 Hz); ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 170.5, 165.6, 163.1, 160.4, 157.8, 138.4, 129.2, 124.8, 120.8, 112.1, 74.1, 63.3, 55.3, 31.4, 8.2 ppm; MS (ESI): *m*/*z*: 366 $[M+Na]^+$; elemental analysis calcd (%) for $C_{17}H_{17}N_3O_5$: C 59.47, H 4.99, N 12.24; found: C 59.21, H 5.07, N 11.97.

(*S*)-8-Ethyl-8-hydroxy-4,7-dioxo-*N*-phenyl-4,5,7,8-tetrahydro-3*H*-pyrano-[4,3-d]pyrimidine-2-carboxamide (26): Chlorotrimethylsilane (0.21 mL, 2.43 mmol) was slowly added to a solution of **24** (0.52 g, 1.52 mmol) and NaI (0.41 g, 2.43 mmol) in CH_3CN (15 mL) and water (14 μL, 0.76 mmol). The mixture was heated in the dark at 65 °C and monitored by TLC. The reaction mixture was quenched by adding a mixture of 5 % Na_2SO_3 and brine (1:1, 10 mL). The mixture was quickly extracted with AcOEt (3 × 20 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (CH_2Cl_2/CH_3OH 60:1) on silica gel gave **26** (0.48 g, 98 %) as a yellow solid. $[\alpha]_D^{19}$ = 29 (*c* = 1.0 in $CHCl_3$/CH_3OH 3:1). M.p. 176–178 °C; IR (KBr): $\tilde{\nu}$ = 3406, 3228, 1678, 1547, 1446, 1252, 1162, 1047, 948, 827, 760 cm^{-1}; ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 13.30 (1H, br s), 10.70 (1H, s), 7.80–7.77 (2H, m), 7.44 (2H, t, *J* = 7.8 Hz), 7.24–7.19 (1H, m), 6.12 (1H, s), 5.31 (1H, AB, *J* = 16.8 Hz), 5.25 (1H, AB, *J* = 16.8 Hz), 2.01–1.84 (2H, m), 0.85 ppm (3H, t, *J* = 7.4 Hz); ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 170.4, 159.2, 157.2, 156.6, 150.4, 137.6, 129.3, 125.3, 121.0, 118.1, 73.0, 64.2, 31.6, 8.2 ppm; MS (ESI): *m*/*z*: 328 $[M-H]^-$; elemental analysis calcd (%) for $C_{16}H_{15}N_3O_5 \cdot 2H_2O$: C 52.60, H 5.24, N 11.50; found: C 52.74, H 5.10, N 11.49.

(*S*)-8-Ethyl-4,7-dioxo-2-(phenylcarbamoyl)-4,5,7,8-tetrahydro-3*H*-pyrano-[4,3-d]pyrimidin-8-yl acetate (27): Acetic anhydride (0.069 mL, 0.729 mmol), pyridine (0.074 mL, 0.912 mmol), and DMAP (7.4 mg, 0.061 mmol) were successively added to a solution of **26** (0.20 g, 0.61 mmol) in dichloromethane (5 mL). The above solution was stirred at room temperature for 2 h. The solvents were removed in vacuo and the residue was purified by silica-gel flash chromatography (CH_2Cl_2/CH_3OH 80:1) to afford **27** (0.20 g, 93 %) as a white solid. $[\alpha]_D^{19}$ = −29 (*c* = 1.0 in $CHCl_3$/CH_3OH 3:1). M.p. 204–206 °C; IR (KBr): $\tilde{\nu}$ = 3358, 3232, 1753, 1689, 1540, 1460, 1257, 1147, 1076, 1032, 944, 825, 760, 692 cm^{-1}; ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 10.38 (1H, s), 7.78–7.75 (2H, m), 7.45–7.39 (2H, m), 7.23–7.18 (1H, m), 5.38 (1H, AB, *J* = 17.1 Hz), 5.30 (1H, AB, *J* = 17.1 Hz), 2.33–2.09 (5H, m), 0.87 ppm (3H, t, *J* = 7.5 Hz); ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 170.3, 167.7, 158.9, 157.6, 153.8, 151.3, 137.5, 129.2, 125.4, 121.4, 118.8, 76.2, 64.8, 29.4, 20.6, 7.7 ppm; MS (ESI): *m*/*z*: 370 $[M-H]^-$; elemental analysis calcd (%) for $C_{18}H_{17}N_3O_6$: C 58.22, H 4.61, N 11.32; found: C 58.28, H 4.64, N 11.27.

(*S*)-3-Allyl-8-ethyl-4,7-dioxo-2-(phenylcarbamoyl)-4,5,7,8-tetrahydro-3*H*-pyrano[4,3-d]pyrimidin-8-yl acetate (31): Potassium carbonate (37 mg, 0.27 mmol) was added to a suspension of **27** (50 mg, 0.14 mmol) in water (0.01 mL) and toluene (1 mL) at 0 °C. After the mixture had been stirred at the same temperature for 10 min, lithium bromide (28 mg, 0.27 mmol) and tetrabutylammonium bromide (4 mg, 0.014 mmol) were added. The whole mixture was stirred for 10 min at room temperature. Allyl methanesulfonate (30 mg, 0.22 mmol) was then added. The reaction mixture was heated to 80 °C and stirred for 2 h. The inorganic residue was removed by filtration over a pad of Celite and washed with CH_2Cl_2. The filtrate and washings were combined and concentrated under reduced pressure. Flash chromatography on silica gel (CH_2Cl_2/CH_3OH 80:1) gave a mixture of **31** and **32** (53 mg, 95 %).

$[PdCl_2(PhCN)_2]$ (2.5 mg, 6.5 μmol) was added to the mixture of **31** and **32** (53 mg, 0.13 mmol) in CH_2Cl_2 (1.3 mL) under a N_2 atmosphere. The reaction mixture was stirred at RT for 2 h. The solvent was evaporated. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/CH_3OH 80:1) to afford **31** as a white solid (53 mg, 100 %). M.p. 84–86 °C; $[\alpha]_D^{19}$ = 9 (*c* = 1.8 in $CHCl_3$/CH_3OH 3:1); IR (KBr): $\tilde{\nu}$ = 3302, 2933, 1168, 1750, 1687, 1599, 1537, 1491, 1435, 1368, 1236, 1094, 1055, 985, 945, 758, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.34 (1H, s), 7.64–7.61 (2H, m), 7.46–7.41 (2H, m), 7.28–7.23 (1H, m), 6.08–5.99 (1H, m), 5.51–5.26 (6H, m), 2.31–2.17 (5H, m), 0.98 ppm (3H, t, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 170.0, 167.0, 158.2, 156.9, 151.7, 150.7, 136.2, 131.6, 129.3, 125.7, 120.0, 119.6, 118.2, 75.7, 64.9, 46.7, 30.2, 20.4, 7.5 ppm;

HRMS (MALDI): m/z: calcd for $C_{21}H_{22}N_3O_6$: 412.1503 $[M+H]^+$; found: 412.1521.

(*S*)-20-*O*-acetyl-14-aza-camptothecin (30): Trifluoromethanesulfonic anhydride (0.055 mL, 0.33 mmol) was slowly added to a solution of triphenylphosphane oxide (0.18 g, 0.66 mmol) in dry CH_2Cl_2 (2 mL) at 0 °C. After this mixture had been stirred at 0 °C for 15 min, **31** (0.090 g, 0.22 mmol) in dry CH_2Cl_2 (1 mL) was added at the same temperature. The reaction was allowed to warm to room temperature and was then stirred for 6 h. Freshly prepared MnO_2 (0.038 g, 0.44 mmol) was then added, and the mixture was stirred at RT for 0.5 h. The solid was removed by filtration over a pad of Celite and was washed with CH_2Cl_2. The filtrate and washings were combined and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/CH_3OH 80:1) to afford **30** (76 mg, 89 %). M.p. 295–297 °C (dec.); $[\alpha]_D^{19}=-27$ ($c=0.4$ in $CHCl_3$/CH_3OH 3:1); IR (KBr): $\tilde{\nu}=$ 3442, 2987, 1691, 1624, 1560, 1385, 1248, 1051, 777, 735 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta=8.51$–8.48 (2H, m), 8.01 (1H, d, $J=7.8$ Hz), 7.90 (1H, t, $J=7.4$ Hz), 7.76 (1H, t, $J=7.4$ Hz), 5.64 (1H, AB, $J=17.1$ Hz), 5.38 (1H, AB, $J=17.1$ Hz), 5.27 (2H, s), 2.41 (2H, q, $J=7.2$ Hz), 2.33 (3H, s), 1.00 ppm (3H, t, $J=7.5$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=$ 170.5, 167.7, 157.9, 157.2, 156.7, 150.1, 149.4, 131.6, 131.0, 130.7, 129.05, 129.01, 128.7, 128.0, 115.7, 76.7, 64.7, 47.5, 30.2, 20.5, 7.5 ppm; MS (ESI): m/z: 414 $[M+Na]^+$; elemental analysis calcd (%) for $C_{21}H_{17}N_3O_5$: C 64.45, H 4.38, N 10.74; found: C 64.21, H 4.34, N 10.99.

(*S*)-14-Aza-camptothecin (5): Concentrated hydrochloric acid (0.3 mL) was added to a solution of **30** (30 mg, 0.077 mmol) in EtOH (1.2 mL). The reaction was stirred at 80 °C for 24 h. The solvents were removed in vacuo and the residue was purified by silica-gel flash chromatography to afford **5** (25 mg, 95 %) in >99 % *ee* (HPLC conditions: Chiralcel AD-H column (0.46×15 cm), *n*-hexane/*i*PrOH 50:50 as mobile phase, flow rate: 1 mL min^{-1}, UV detection at 254 nm; t_R ((*S*)-isomer): 11.1, t_R ((*R*)-isomer): 12.5 min). M.p. 272–294 °C (dec.); $[\alpha]_D^{20}=24$ ($c=1.2$ in $CHCl_3$/CH_3OH 3:1).[25] IR (KBr): $\tilde{\nu}=3358$, 2927, 1757, 1649, 1596, 1542, 1500, 1431, 1349, 1206, 1157, 1100, 924, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta=8.55$ (1H, s), 8.47 (1H, d, $J=8.4$ Hz), 8.02 (1H, d, $J=8.7$ Hz), 7.92 (1H, dt, $J=6.9$, 1.2 Hz), 7.78 (1H, dt, $J=8.1$, 1.2 Hz), 5.63 (1H, AB, $J=$ 16.8 Hz), 5.32 (2H, s), 5.30 (1H, AB, $J=16.8$ Hz), 4.11 (1H, s), 2.10–2.02 (2H, m), 1.10 ppm (3H, t, $J=7.5$ Hz); ^{13}C NMR ([D_6]DMSO, 75 MHz): $\delta=171.9$, 159.4, 157.8, 157.4, 151.3, 148.6, 132.3, 131.3, 131.0, 130.0, 128.87, 128.85, 128.77, 114.9, 73.7, 63.9, 48.4, 30.8, 8.5 ppm; MS (ESI): m/z: 348 $[M-H]^-$; elemental analysis calcd (%) for $C_{19}H_{15}N_3O_4$: C 65.32, H 4.33, N 12.03; found: C 65.37, H 4.31, N 11.89.

Acknowledgements

Financial support from MOST (2010CB833200), MOH (2009ZX09501), and CAS (KSCX2-YW-R23, KJCX2-YW-H08) are greatly appreciated.

[1] a) M. E. Wall, M. C. Wani, C. E. Cook, K. H. Palmer, A. T. McPhail, G. A. Sim, *J. Am. Chem. Soc.* **1966**, *88*, 3888; b) M. E. Wall, *Med. Res. Rev.* **1998**, *18*, 299.

[2] a) C. G. Moertel, A. J. Schutt, R. J. Reitemeier, R. G. Hahn, *Cancer Chemother. Rep.* **1972**, *56*, 95; b) Y. H. Hsiang, L. F. Liu, M. E. Wall, M. C. Wani, A. W. Nicholas, G. Manikumar, S. Kirschenbaum, R. Silber, M. Potmesil, *Cancer Res.* **1989**, *49*, 4385.

[3] For recent reviews on the chemistry and biology of the camptothecin alkaloids, see: a) M. E. Wall, M. C. Wani, *Alkaloids* **1998**, *50*, 509; b) "The Camptothecins: from Discovery to the Patient," P. Pantaziz, B. C. Giovanella, *Ann. N. Y. Acad. Sci.* **1996**, *803*, 1–335; c) "Antitumor Alkaloids in Clinical Use or in Clinical Trials," M. Cuendet, J. M. Pezzuto in *Modern Alkaloids: Structure, Isolation, Synthesis and Biology* (Eds.: E. Fattorusso, O. Taglialatela-Scafati), Wiley-VCH, Weinheim, **2008**, pp. 29–33; d) C. J. Thomas, N. J. Rahier, S. M. Hecht, *Bioorg. Med. Chem.* **2004**, *12*, 1585; e) W. Du, *Tetrahedron* **2003**, *59*, 8649.

[4] L. Z. Lin, G. A. Cordell, *Phytochemistry* **1989**, *28*, 1295.

[5] Z. Z. Ma, Y. Hano, T. Nomura, Y. J. Chen, *Heterocycles* **1997**, *46*, 541.

[6] W. D. Kingsbury, J. C. Boehm, D. R. Jakas, K. G. Holden, S. M. Hecht, G. Gallagher, M. J. Caranfa, F. L. McCabe, L. F. Faucette, R. K. Johnson, R. P. Hertzberg, *J. Med. Chem.* **1991**, *34*, 98.

[7] a) S. Negoro, M. Fukuoka, N. Masuda, M. Takada, Y. Kusunoki, K. Matsui, N. Takifuji, S. Kudoh, H. Niitani, T. Taguchi, *J. Natl. Cancer Inst.* **1991**, *83*, 1164; b) Y. Kawato, M. Aonuma, Y. Hirota, H. Kuga, K. Sato, *Cancer Res.* **1991**, *51*, 4187.

[8] a) G. M. Cragg, D. J. Newman, *J. Nat. Prod.* **2004**, *67*, 232; b) M. S. Butler, *Nat. Prod. Rep.* **2005**, *22*, 162.

[9] K. J. Cheng, N. J. Rahier, B. M. Eisenhauer, R. Gao, S. J. Thomas, S. M. Hecht, *J. Am. Chem. Soc.* **2005**, *127*, 838.

[10] N. J. Rahier, K. J. Cheng, R. Gao, B. M. Eisenhauer, S. M. Hecht, *Org. Lett.* **2005**, *7*, 835.

[11] M. A. Elban, W. Y. Sun, B. M. Eisenhauer, R. Gao, S. M. Hecht, *Org. Lett.* **2006**, *8*, 3513.

[12] J. B. Hendrickson, S. M. Schwartzman, *Tetrahedron Lett.* **1975**, *16*, 277.

[13] For representative applications of the Hendrickson reagent, see: a) S. L. You, H. Razavi, J. W. Kelly, *Angew. Chem.* **2003**, *115*, 87; *Angew. Chem. Int. Ed.* **2003**, *42*, 83; b) S. L. You, J. W. Kelly, *J. Org. Chem.* **2003**, *68*, 9506; c) S. L. You, J. W. Kelly, *Org. Lett.* **2004**, *6*, 1681; d) Q. L. Dong, G. S. Liu, H. B. Zhou, L. Chen, Z. J. Yao, *Tetrahedron Lett.* **2008**, *49*, 1636.

[14] a) H. B. Zhou, G. S. Liu, Z. J. Yao, *Org. Lett.* **2007**, *9*, 2003; b) H. B. Zhou, G. S. Liu, Z. J. Yao, *J. Org. Chem.* **2007**, *72*, 6270.

[15] For Fortunak's synthesis of the core structure of camptothecin, see: J. M. D. Fortunak, A. R. Mastrocola, M. Mellinger, N. J. Sisti, J. L. Wood, Z. P. Zhuang, *Tetrahedron Lett.* **1996**, *37*, 5679.

[16] H. Josien, S. B. Ko, D. Bom, D. P. Curran, *Chem. Eur. J.* **1998**, *4*, 67.

[17] I. Ricoh, K. Halvorsen, C. Dubrule, A. J. Lattes, *J. Org. Chem.* **1994**, *59*, 415.

[18] S. P. Chavan, M. S. Venkatraman, *ARKIVOC* **2005**, 165.

[19] G. S. Liu, Q. L. Dong, Y. S. Yao, Z. J. Yao, *Org. Lett.* **2008**, *10*, 5393.

[20] a) H. C. Kolb, M. S. Vannieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483; b) G. A. Crispino, K. S. Jeong, H. C. Kolb, Z. M. Wang, D. Xu, K. B. Sharpless, *J. Org. Chem.* **1993**, *58*, 3785.

[21] Z. X. Wang, Y. Tu, M. Frohn, J. R. Zhang, Y. A. Shi, *J. Am. Chem. Soc.* **1997**, *119*, 11224.

[22] K. Itami, D. Yamazaki, J. I. Yoshida, *Org. Lett.* **2003**, *5*, 2161.

[23] N. Ototake, M. Nakamura, Y. Dobashi, H. Fukaya, O. Kitagawa, *Chem. Eur. J.* **2009**, *15*, 5090.

[24] X. Q. Dai, C. Cheng, C. Y. Ding, Q. Z. Yao, A. Zhang, *Synlett* **2008**, *19*, 2989.

[25] The optical rotation of (*S*)-14-azacamptothecin was not reported in reference [10].

Received: January 26, 2010
Published online: May 18, 2010

