Synthetic Studies on Camptothecins

Part 1

An Improved Asymmetric Total Synthesis of (20*S*)-Camptothecin

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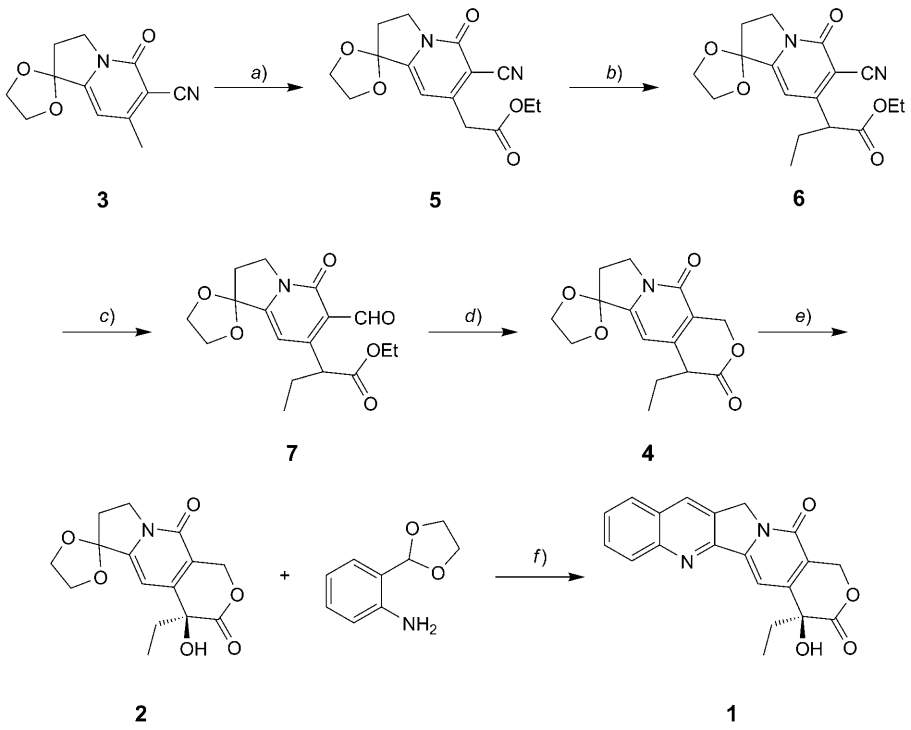
A six-step asymmetric total synthesis of (20*S*)-camptothecin (**1**) has been accomplished in 25% overall yield starting from the known pyridone **3**. The key steps in this synthesis are the chemoselective Ni-catalyzed hydrogenation of 3-cyanopyridone **6** to 3-formylpyridone **7** in AcOH/pyridine/H_2O and the *Davis* asymmetric hydroxylation of tricyclic lactone **4** utilizing a chiral *N*-sulfonyloxaziridine into (4′*S*)-tricyclic hydroxylactone **2**.

Introduction. – Since its first isolation from the Chinese plant *Camptotheca acuminate* by *Wall* and co-workers in 1966 [1], (20*S*)-Camptothecin (CPT, **1**) has attracted intense interest as a synthetic target over the past decades due to its unique chemical structure and potent antitumor activity. Although (20*S*)-camptothecin can not be used as a drug because of its poor water-solubility and severe side effects, this alkaloid continues to serve as a very attractive and promising lead compound in the development of new anticancer (20*S*)-camptothecins drugs. Accordingly, a number of strategies have so far been developed for the asymmetric synthesis of **1** [2], and the *Friedländer* approach implying the (4′*S*)-tricyclic hydroxylactone **2** as a key chiral building block seems to be most attractive. To date, three approaches have been disclosed for this chiral intermediate including the use of a chiral auxiliary group [3], asymmetric dihydroxylation [4], and chemical and enzymatic resolutions [5] as key steps. However, these methods suffered either from the use of stoichiometric amounts of expensive chiral auxiliaries, application of highly toxic reagents, or low efficiency of optical resolution. Therefore, the development of an efficient and practical preparation of **2** is still in demand. Herein, we describe an efficient asymmetric total synthesis of **1** starting from the known pyridone **3** *via* the chiral *N*-sulfonyloxaziridine-mediated asymmetric hydroxylation [6] of **4** into (4′*S*)-tricyclic hydroxylactone **2** as the key step.

Results and Discussion. – Our present synthetic route to **1** is outlined in the *Scheme*. The known pyridone **3** was prepared in the overall yield of 30.8% from ethyl 2-ethoxy-4-oxopent-2-enoate following the known protocol [7]. Carbonylation of **3** with diethyl carbonate in the presence of a catalytic amount of EtONa or MeONa in anhydrous THF gave the corresponding ester **5** in 90% yield. Although high-yielding ethylation of **5** under *Wani*'s condition (EtI/*t*-BuOK) [8] was reported, this procedure is impractical

for large-scale synthesis due to the low temperature (– 78°). Fortunately, we found that compound **5** reacted with EtBr and K_2CO_3 in MeCN under reflux for 3 h to give 3-cyanopyridone **6** in 95% yield, which was subjected to *Raney*-Ni-catalyzed hydrogenation in AcOH/pyridine/H_2O (1:1:1) to furnish 3-formylpyridone **7** in 60% yield. Reduction of **7** with $NaBH_4$ in MeOH at – 20° for 3 h, followed by lactonization with 10% aqueous HCl at the same temperature for 1 h, then room temperature for another 2 h led to the racemic tricyclic lactone **4** in 91% yield.

Scheme



a) MeONa, $CO(OEt)_2$, THF, reflux, 5 h, 90%. *b*) EtBr, K_2CO_3, MeCN, reflux, 3 h, 95%. *c*) H_2, *Raney*-Ni, AcOH, pyridine, H_2O, 50°, 6 h, 60%. *d*) 1. $NaBH_4$, MeOH, – 20°, 3 h; 2. 10% HCl, – 20°, 1 h, then r.t., 2 h, 91%. *e*) 1. KHMDS, (4a*S*,7*S*,8a*R*)-tetrahydro-8,8-dimethoxy-9,9-dimethyl-4*H*-4a,7-methanooxazirino[3,2-*i*][2,1]benzisothiazole 3,3-dioxide, THF, CH_2Cl_2, HMPA, – 78°, 12 h; 2. sat. NH_4Cl soln., – 78°, 10 min, 82% (72% ee). *f*) conc. HCl, EtOH, reflux, 4 h, 66%.

With **4** in hand, our next concern was to assemble the OH group with (*S*)-configuration at the C(4′) position in **4** utilizing the *Davis* asymmetric hydroxylation protocol [9]. Initially, when **4** was treated with various bases (LHMDS, NHMDS, KHMDS and LDA) and *Davis* reagent (=(4a*S*,7*S*,8a*R*)-tetrahydro-8,8-dimethoxy-9,9-dimethyl-4*H*-4a,7-methanooxazirino[3,2-*i*][2,1]benzisothiazole 3,3-dioxide) [10] in different solvents (THF, THF/PhMe, THF/HMPA, and THF/PhMe/HMPA), only 4–9% of (4′*S*)-tricyclic hydroxylactone **2** was isolated. Interestingly, treatment of **4** with KHMDS and the above mentioned chiral *N*-sulfonyloxaziridine in THF/CH_2Cl_2/

HMPA at $-78°$ for 12 h led successfully to **2** in 82% yield (72% ee). Unfortunately, all attempts to improve the optical purity of **2** by recrystallization from different solvents were unsuccessful. In the final step, the *Friedländer* condensation between **2** and 2-(1,3-dioxolan-2-yl)aniline in the presence of conc. HCl in EtOH provided (20*S*)-camptothecin **1** in 66% yield.

Conclusions. – In conclusion, an improved process for the preparation of (4′*S*)-tricyclic hydroxylactone **2** *via* chiral *N*-sulfonyloxaziridine-mediated asymmetric hydroxylation resulted in a short synthesis of (20*S*)-camptothecin (**1**) in 25% overall yield starting from the known pyridone **3**. Further studies on asymmetric syntheses of other camptothecin drugs and their analogues *via* the key chiral intermediate **2** are currently underway.

Experimental Part

General. Reagents and chemicals were obtained from commercial suppliers and used without further purification. THF was distilled from Na/benzophenone. CH_2Cl_2 and HMPA were distilled from CaH_2. AcOEt and petroleum ether (PE) for column chromatography (CC) were distilled before use. M.p. uncorrected; *WRS-1B* digital melting-point apparatus. TLC: Aluminium-backed silica gel *60* F_{254} plates. HPLC: *Shimadzu-LC-10AT* liquid chromatograph with *Spd-10A* UV/VIS detector, working at 270 nm; *Supelco-C18* column (150×4.6 mm), elution with MeCN/H_2O 50:50 at a flow rate 1.0 ml/min; *Chiralcel OD-H* column (250×4.6 mm), elution with hexane/i-PrOH 70:30 at a flow rate 0.5 ml/min. Optical rotations: *Jasco P1020* digital polarimeter. IR Spectra: *Jasco FT/IR-4200* spectrometer. ^{1}H- and ^{13}C-NMR spectra: *Bruker Avance-400* spectrometer; at 400 (^{1}H) and 100 (^{13}C) MHz; in $CDCl_3$ or (D_6)DMSO with $CHCl_3$ (δ(H) 7.24) or DMSO (δ(H) 2.49) and $CDCl_3$ (δ(C) 77.0) or DMSO (δ(C) 39.5) as internal standards; δ in ppm, J in Hz. MS: *Waters Quattro-Micromass* instrument; electrospray ionization (ESI) techniques; in m/z.

*Ethyl (6′-Cyano-2′,3′-dihydro-5′-oxo-5′*H*-spiro[1,3-dioxolane-2,1′-indolizin]-7′-yl)acetate* (**5**). To a suspension of MeONa (4.86 g, 90 mmol) in anh. THF (80 ml) was added **3** (4.64 g, 20 mmol) at r.t. (25°). After stirring for 10 min, diethyl carbonate (9.44 g, 80 mmol) was added dropwise within 10 min. The mixture was refluxed for further 5 h, then cooled to r.t. and poured cautiously into ice-water followed by addition of 10% aq. HCl (30 ml). The resulting mixture was extracted with CH_2Cl_2 (3×50 ml) and the org. phase was washed with 10% $NaCO_3$ (3×50 ml) and brine (3×20 ml), and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave the crude product, which was recrystallized from MeOH to afford pure **5** (5.47 g, 90%) as a pea green solid. M.p. 172–173° ([8]: m.p. 172–173°). IR (KBr): 2982, 2895, 2220, 1735, 1655, 1600, 1535, 1198, 1094, 1028, 947. ^{1}H-NMR ($CDCl_3$): 6.39 (*s*, H–C(5)); 4.08–4.19 (*m*, 2 CH_2O, CH_2N, MeCH_2O); 3.80 (*s*, CH_2CO); 2.36 (*t*, $J = 12$, CH_2CH_2N); 1.24 (*t*, $J = 12$, Me). ESI-MS: 305 ($[M+H]^+$).

*Ethyl 2-(6′-Cyano-2′,3′-dihydro-5′-oxo-5′*H*-spiro[1,3-dioxolane-2,1′-indolizin]-7′-yl)butanoate* (**6**). A mixture of **5** (6.08 g, 20 mmol), K_2CO_3 (6.90 g, 50 mmol), and EtBr (3.93 g, 36 mmol) in MeCN (100 ml) was stirred under reflux for 3 h. After cooling to r.t., the precipitate was filtered and washed with MeCN. Evaporation of the solvent under reduced pressure gave the crude product **6** (6.30 g, 95%), which could be directly used for the next step. A small sample was recrystallized from EtOH. M.p. 121–122° ([7b]: m.p. 122–123°). IR (KBr): 2964, 2854, 2222, 1732, 1653, 1558, 1458, 1367, 1236, 1093, 945, 845. ^{1}H-NMR ($CDCl_3$): 6.33 (*s*, H–C(5)); 4.07–4.14 (*m*, 2 CH_2O, CH_2N, MeCH_2O); 3.85 (*t*, $J = 16$, CHCO); 2.33 (*t*, $J = 12$, CH_2CH_2N); 1.60–1.66, 2.04–2.11 (2*m*, MeCH_2); 0.90, 1.19 (2*t*, 2 Me). ESI-MS: 333 ($[M+H]^+$).

*Ethyl 2-(6′-Formyl-2′,3′-dihydro-5′-oxo-5′*H*-spiro[1,3-dioxolane-2,1′-indolizin]-7′-yl)butanoate* (**7**). A soln. of **6** (3.32 g, 10 mmol) in pyridine (15 ml), AcOH (15 ml), and H_2O (15 ml) was hydrogenated in the presence of *Raney*-Ni (6.50 g) at 50° under 1 atm for 6 h. The progress of this reaction was followed by TLC (AcOEt/CH_2Cl_2 1:4). The Ni catalyst was removed by filtration, and the solvent was removed

under reduced pressure. The residue was diluted with CH_2Cl_2 (60 ml) and the org. phase was washed with 10% aq. HCl (3×20 ml), 10% $NaCO_3$ (3×20 ml), and brine (3×20 ml), and dried ($NaSO_4$). Evaporation of the solvent under reduced pressure gave the crude product, which was recrystallized from EtOH to afford pure **7** (2.00 g, 60%) as a white solid. M.p. 85–86°. IR (KBr): 2976, 2883, 2844, 1734, 1683, 1648, 1593, 1529, 1440, 1338, 1266, 1189, 1021, 939, 844. ^{1}H-NMR ($CDCl_3$): 10.50 (*s*, CHO); 6.36 (*s*, H–C(5)); 5.04 (*t*, *J* = 16, CHCO); 4.09–4.20 (*m*, 2 CH_2O, CH_2N, MeCH_2O); 2.41 (*t*, *J* = 12, CH_2CH_2N); 0.91, 1.20 (*2t*, 2 Me). ^{13}C-NMR ($CDCl_3$): 191.69; 171.92; 161.86; 157.51; 153.11; 120.98; 112.59; 99.24; 65.26; 65.22; 60.46; 46.15; 44.41; 33.11; 25.68; 13.62; 11.44. ESI-MS: 336 ($[M+H]^+$).

*4′-Ethyl-1′,4′,7′,8′-tetrahydro-3′*H,*10′*H-*spiro[1,3-dioxolane-2,6′-pyrano[3,4-f]indolizine]-3′,10′-dione* (**4**). To a soln. of **7** (1.68 g, 5 mmol) in MeOH (30 ml) was added slowly $NaBH_4$ (0.29 g, 7.5 mmol) at −20°. The mixture was stirred at this temp. for 3 h before adding 10% aq. HCl (8 ml) over a period of 5 min. Stirring was continued at −20° for 1 h, then the mixture was gradually warmed to 25° and stirred for another 2 h. The mixture was evaporated *in vacuo* and the residue was diluted with CH_2Cl_2 (30 ml). The org. phase was washed with 10% $NaCO_3$ (3×20 ml) and brine (3×20 ml), and dried ($NaSO_4$). Evaporation of the solvent gave the crude product, which was recrystallized from AcOEt/hexane to afford pure **4** (1.32 g, 91%) as a white solid. M.p. 126–127° ([5a]: m.p. 130°). IR (KBr): 2978, 2896, 1749, 1663, 1614, 1457, 1306, 1219, 1164, 1062, 937, 822. ^{1}H-NMR ($CDCl_3$): 6.05 (*s*, H–C(5)); 5.17, 5.40 (*2d*, *J* = 16, CH_2OCO); 4.04–4.14 (*m*, 2 CH_2O, CH_2N); 3.37 (*t*, *J* = 16, CHCO); 2.34 (*t*, *J* = 12, CH_2CH_2N); 1.85–1.94 (*m*, MeCH_2); 0.96 (*t*, *J* = 12, Me). ESI-MS: 292 ($[M+H]^+$).

*(4′*S*)-4′-Ethyl-1′,4′,7′,8′-tetrahydro-4′-hydroxy-3′*H,*10′*H-*spiro[1,3-dioxolane-2,6′-pyrano[3,4-f]indolizine]-3′,10′-dione* (**2**). Under the atmosphere of Ar, KHMDS (4.50 ml, 3.980 mmol, 0.885M soln. in toluene) was slowly added to a soln. of **4** (463 mg, 1.591 mmol) in anh. THF (15 ml)/CH_2Cl_2 (5 ml)/HMPA (6 ml) at −78°. After stirring for 1 h at the same temp., a soln. of (4a*S*,7*S*,8a*R*)-tetrahydro-8,8-dimethoxy-9,9-dimethyl-4*H*-4a,7-methanooxazirino[3,2-*i*][2,1]benzisothiazole 3,3-dioxide (690 mg, 2.387 mmol) in anh. THF (5 ml) and CH_2Cl_2 (5 ml) was added into the mixture at −78° and stirred for 12 h at this temp., then a sat. aq. NH_4Cl soln. (5 ml) was slowly added. After stirring for 10 min, the mixture was warmed gradually to r.t. and poured into H_2O (30 ml). The resulting mixture was extracted with CH_2Cl_2 (2×20 ml), and the combined org. phase was washed with 10% $NaHCO_3$ (2×20 ml) and brine (2×20 ml), and dried (Na_2SO_4). Evaporation of the solvent gave the crude product, which was purified by CC (AcOEt/PE, 1:1) to afford **2** (391 mg, 82%, 72% ee) as a white solid. M.p. 163–164°. $[\alpha]_D^{25} = +76.8$ (*c* = 0.76, $CHCl_3$) ([3]: m.p. 170–171°, $[\alpha]_D^{25} = +109.7$ (*c* = 0.76, $CHCl_3$)). IR (KBr): 3258, 2988, 2969, 1752, 1660, 1594, 1472, 1421, 1377, 1352, 1268, 1115, 1073, 967, 903, 800. ^{1}H-NMR ($CDCl_3$): 6.58 (*s*, H–C(5)); 5.18, 5.62 (*2d*, *J* = 16, CH_2OCO); 4.13–4.21 (*m*, 2 CH_2O, CH_2N); 3.67 (*s*, OH); 2.43 (*t*, *J* = 12, CH_2CH_2N); 1.78–1.82 (*m*, MeCH_2); 0.98 (*t*, *J* = 12, Me). ESI-MS: 308 ($[M+H]^+$).

*(20*S*)-Camptothecin* (= *(4*S*)-4-Ethyl-4-hydroxy-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione*; **1**). A mixture of **2** (0.62 g, 2.0 mmol), 2-(1,3-dioxolan-2-yl)aniline (0.50 g, 3.0 mmol) and 37% aq. HCl soln. (3.0 ml) in EtOH (30 ml) was stirred under reflux for 4 h. After cooling to r.t., the precipitate was filtered. Then the filtrate was adjusted to pH = 7 with sat. aq. $NaHCO_3$, condensed to one third of its volume and filtered. The crude product was recrystallized from 80% AcOH to afford pure (20*S*)-camptothecin **1** (0.46 g, 66%) as a yellow solid. M.p. 261–263° (dec.). $[\alpha]_D^{25} = +32.4$ (*c* = 0.51, $CHCl_3$/MeOH 4:1) ([3][5a]: m.p. 265–266° (dec.), $[\alpha]_D = +42.0$ (*c* = 0.51, $CHCl_3$/MeOH 4:1)).

REFERENCES

[1] 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.

[2] C. R. Hutchinson, *Tetrahedron* **1981**, *37*, 1047; W. Du, *Tetrahedron* **2003**, *59*, 8649.

[3] A. Ejima, H. Terasawa, M. Sugimori, H. Tagawa, *J. Chem. Soc., Perkin Trans. 1* **1990**, 27.

[4] S.-S. Jew, K.-D. Ok, H.-J. Kim, M. G. Kim, J. M. Kim, J. M. Hah, Y.-S. Cho, *Tetrahedron: Asymmetry* **1995**, *6*, 1245.

[5] a) H. Terasawa, M. Sugimori, A. Ejima, H. Tagawa, *Chem. Pharm. Bull.* **1989**, *37*, 3382; b) A. Imura, M. Itoh, A. Miyadera, *Tetrahedron: Asymmetry* **1998**, *9*, 2285.

[6] F. A. Davis, B. C. Chen, *Chem. Rev.* **1992**, *92*, 919; P. Zhou, B. C. Chen, F. A. Davis, 'Asymmetric Oxidation Reactions', Oxford University Press, 2001, p. 128.
[7] a) M. E. Wall, M. C. Wani, A. W. Nicholas, G. Manikumar, U.S. Pat. 4894456, 1990; b) Shanghai No. 5 Pharmaceutical Plant, *Sci. Sin*. **1978**, *21*, 87.
[8] M. C. Wani, P. E. Ronman, J. T. Lindley, M. E. Wall, *J. Med. Chem.* **1980**, *23*, 554.
[9] K. Hiroya, K. Kawamoto, T. Sakamoto, *Synlett* **2006**, 2636; K. Tagami, N. Nakazawa, S. Sano, Y. Nagao, *Heterocycles* **2000**, *53*, 771; F. A. Davis, A. Kumar, *J. Org. Chem.* **1992**, *57*, 3337; F. A. Davis, A. Kumar, B.-C. Chen, *Tetrahedron Lett.* **1991**, *32*, 867; A. B. Smith, G. A. Sulikowski, K. Fujimoto, *J. Am. Chem. Soc.* **1989**, *111*, 8039.
[10] J. C. Towson, M. C. Weismiller, G. S. Lal, A. C. Sheppard, A. Kumar, F. A. Davis, *Org. Synth.* **1993**, *Coll. Vol. 8*, 104; B.-C. Chen, C. K. Murphy, A. Kumar, R. T. Reddy, C. Clark, P. Zhou, B. M. Lewis, D. Gala, I. Mergelsberg, D. Scherer, J. Buckley, D. DiBenedetto, F. A. Davis, *Org. Synth.* **1998**, *Coll. Vol. 9*, 212.

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