Synthetic Studies on Camptothecins

Part 3[1])

Total Synthesis of (20*S*)-7-Ethyl-10-hydroxycamptothecin *via* a Bifunctional Thiourea-Based Cinchona Alkaloid-Mediated Enantioselective Cyanosilylation Strategy

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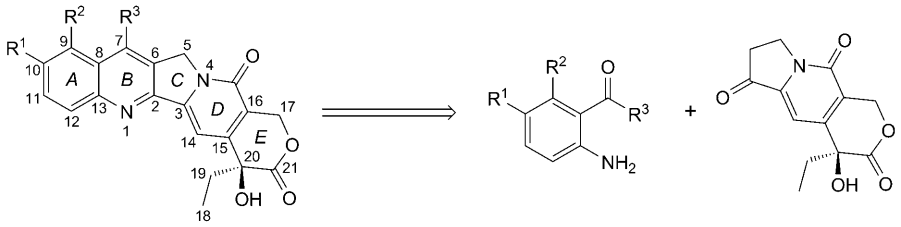
A concise and efficient asymmetric process for the total synthesis of (20*S*)-7-ethyl-10-hydroxycamptothecin (= SN-38; **1f**), an active metabolic form of the prodrug irinotecan, is described. This approach features the enantioselective cyanosilylation of indolizinone **4** into the corresponding cyanohydrin **5**, mediated by a bifunctional thiourea-based cinchona alkaloid under mild conditions, and I_2-catalyzed *Friedländer* condensation of the tricyclic lactone **6** and 2-amino-5-hydroxy propiophenone (= 1-(2-amino-5-hydroxyphenyl)propan-1-one).

Introduction. – Since the unique mechanism of action as selective inhibitor of DNA topoisomerase I was discovered [3], (20*S*)-camptothecin (= CPT = (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; **1a**) has become a fascinating and most useful lead compound for the design of anticancer candidates, which had led to the development of topotecan (**1b**), irinotecan (**1c**), and belotecan (**1d**), as well as other analogues currently in clinical and preclinical trials[2]). In general, substitutions on rings *C*, *D*, and *E* of CPT lead to a potency decrease. On the contrary, the modifications of rings *A* and *B*, especially at C(7), C(9), and C(10), often improved biological activities [5]. So we decided to explore economic and efficient total syntheses of CPT and its derivatives with the tricyclic lactone **6** and ring-*A* precursors *via Friedländer* condensation as shown in *Scheme 1*. This convergent synthetic strategy was expected to make the synthesis of functionalized substitutes of rings *A* and *B* of CPT-derived alkaloids more concise and efficient. In the previously reported approaches including our work, the key chiral building block **6** has been obtained through *Davis* asymmetric hydroxylation [1a], *Sharpless* asymmetric dihydroxylation [1b], diastereoselective ethylation [1c], or a kinetic-resolution strategy [1d–1h]. However, these methods required, for the asymmetric reaction, harsh conditions, the utilization of highly toxic catalysts, or the employment of stoichiometric amounts of an expensive chiral auxiliary. Therefore, the development of a more

[1]) For Part 1, see [1a]; for Part 2, see [2].

[2]) For reviews on the development of camptothecin and its derivatives, see [4]. The trivial atom numbering is given in *Scheme 1*; for the systematic name of the target compound **1f**, see *Exper. Part.*

Scheme 1



	R^1	R^2	R^3
1a Camptothecin	H	H	H
1b Topotecan	OH	$MeNCH_2$	H
1c Irinotecan	PipPipCOO	H	Et
1d Belotecan	H	H	$Me_2CHNCH_2CH_2$
1e 10-Hydroxycamptothecin	OH	H	H

6

convenient and practical process for the preparation of (*S*)-lactone **6** is still in high demand.

It is well known that the enantioselective cyanosilylation of a ketone is a very important approach for the preparation of cyanohydrins with a quaternary stereogenic center[3]), which usually act as versatile precursors to α-hydroxy acids, β-amino alcohols, and other valuable chiral building blocks. In recent years, the asymmetric cyanosilylation of carbonyl compounds in the presence of 'dual-activation' organic catalysts has provided a powerful tool for the construction of quaternary stereogenic centers, due to high enantioselectivity and mild conditions in a metal-free and environmentally benign system [7]. In continuation of our work on the total synthesis of CPT-family alkaloids, we herein report the first synthesis of **6** by employing an enantioselective cyanosilylation of **4** mediated by a bifunctional thiourea-based cinchona alkaloid as a key step, a chiral building block to complete an efficient total synthesis of SN-38 **1f**.

Results and Discussion. – Our synthetic route to the target compound **1f** (**1**, $R^1 =$ OH, $R^2 = H$, $R^3 = Et$) is depicted in *Scheme 2*. The known formyloxy ketone **2**, obtained as previously described [8], was converted smoothly into hydroxypyridinone **3** in high yield. Silyl ether protection of the free OH group of **3** was chosen over other possible forms of protection, since it was thought that the deprotection and the transformation of cyanide into α-hydroxy acid could be performed in one step. In addition, the ^{t}BuMe$_2$Si protection was also stable under the subsequent reaction conditions. With the indolizinone **4** in hand, the key asymmetric cyanosilylation was next undertaken. At the outset, we chose the powerfully bifunctional thiourea-based cinchona-alkaloid catalyst **7**[4]) which has been widely used in recent years to promote the cyanosilylation of **4**. The optimization of the reaction conditions are illustrated in the *Table*. Initially, different solvents were screened, with 1 mmol of substrate **4** and

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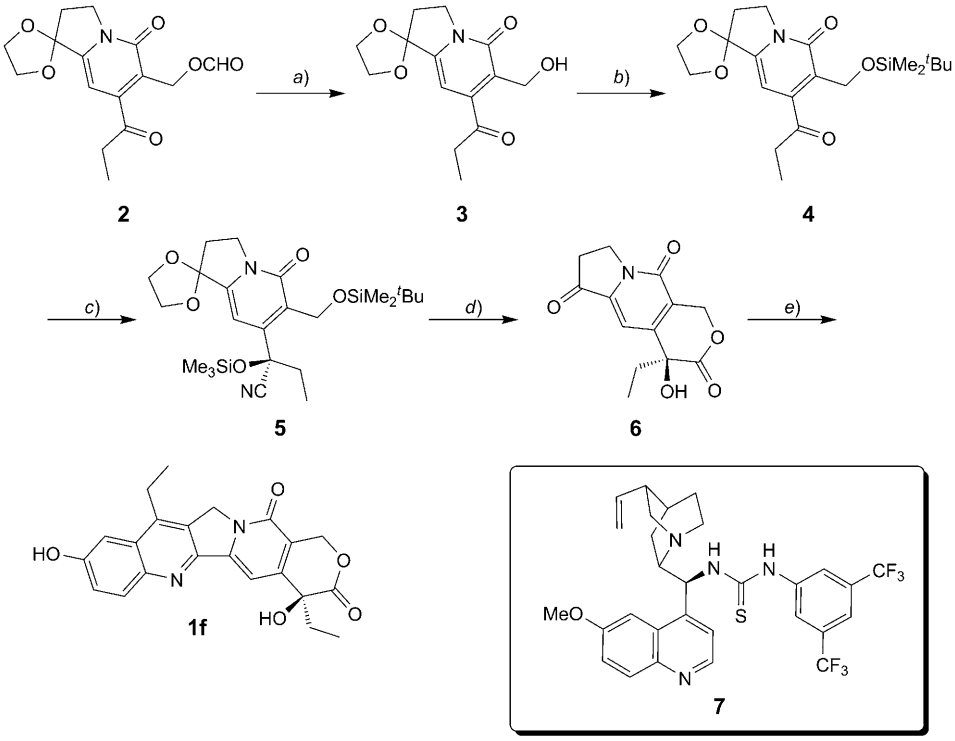
[3]) For reviews on the synthesis of cyanohydrins, see [6].

[4]) The bifunctional thiourea-based cinchona-alkaloid catalyst **7** was prepared according to the procedure described in [9].

Scheme 2

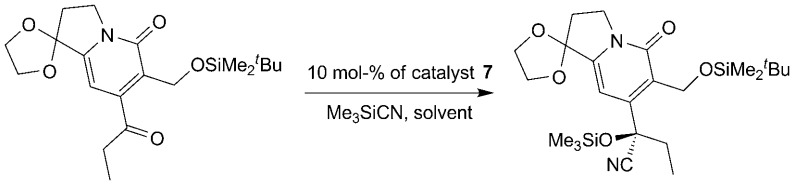


a) $NaHCO_3$, MeOH, H_2O, r.t., 2 h; 93%. *b*) ^{t}BuMe$_2$SiCl, DMAP (= *N*,*N*-dimethylpyridin-4-amine), 1*H*-imidazole, CH_2Cl_2, reflux, 36 h; 90%. *c*) Me_3SiCN, catalyst **7**, CF_3CH_2OH, CH_2Cl_2, $-10°$, 80 h; 85%. *d*) Sat. HCl(g), EtOH, 90°, 3 h; 60% (65% ee). *e*) 1-(2-Amino-5-hydroxyphenyl)propan-1-one, I_2, DMF, 80°, 8 h; 75%.

3 equiv. of Me_3SiCN at room temperature (*Entries 1–4*). The conversion in CH_2Cl_2 was highest because of the good solubility of **4**. The enantioselectivity of the cyanosilylation increased slightly when the reaction temperature was lowered (*Entries 4–7*); however, concomitantly the reaction time was significantly prolonged for a similar conversion yield. To improve the reactivity and selectivity of the cyanosilylation, CF_3CH_2OH was added to the reaction system, an alcohol producing a beneficial effect on carbonyl 1,2-addition reactions in some cases[5]). It is worth mentioning that the enantiomer excess (ee) of lactone **6** was improved to 65%, accompanied by complete substrate conversion (*Entry 8*); usually such a result has been explained by the *in situ* generation of HCN upon adding an alcohol to promote the addition reaction. A further decrease in the reaction temperature resulted in lower conversions and longer reaction times, but the enantiomer excess remained almost

[5]) For examples of the beneficial effect of alcohol additives on carbonyl 1,2-addition reactions, see [7a] and ref. cit. therein.

Table. *Optimization of the Reaction Conditions in the Asymmetric Cyanosilylation of Pyridinone* **4**[a])



4 **5**

Entry	Solvent	Additive	Temp. [°]	Time	Conv. [%]	ee [%][b])
1	Toluene		20	48 h	< 5	–
2	THF		20	48 h	< 5	–
3	^{t}BuOMe		20	48 h	< 10	–
4	CH_2Cl_2		20	48 h	70	30
5	CH_2Cl_2		10	60 h	71	38
6	CH_2Cl_2		0	72 h	69	46
7	CH_2Cl_2		– 10	96 h	73	60
8	CH_2Cl_2	CF_3CH_2OH[c])	– 10	80 h	100	65
9	CH_2Cl_2	CF_3CH_2OH	– 20	5 d	90	67
10	CH_2Cl_2	CF_3CH_2OH	– 40	6 d	88	66

[a]) Reaction conditions: indolizinone **4** (1 mmol), Me_3SiCN (3 mmol), 5 ml of solvent. [b]) Determination based on the enantiomer excess of lactone **6**. [c]) 1.5 equiv. of CF_3CH_2OH was used.

unchanged (*Entries 9* and *10*). Thus, in terms of enantioselectivity and substrate conversion, the cyanosilylation of indolizinone **4** was best performed with Me_3SiCN in the presence of cinchona-alkaloid derivative **7** as catalyst at – 10° for 80 h to give, after column chromatography, the cyanohydrin **5** in 85% yield. The tricyclic lactone **6** was then obtained by treatment of **5** with saturated HCl(g) in EtOH according to *Shibasaki*'s methodology [10] (*Scheme 2*). Finally, the key building block **6** was directly subjected to the *Friedländer* condensation with 2-amino-5-hydroxypropiophenone (=1-(2-amino-5-hydroxyphenyl)propan-1-one)[6]) catalyzed by I_2 to afford (20*S*)-7-ethyl-10-hydroxycamptothecin (**1f**) in 75% yield.

Conclusions. – To summarize, a concise and improved asymmetric total synthesis of (20*S*)-7-ethyl-10-hydroxycamptothecin (**1f**) from the formyloxy ketone **2** was accomplished in 32% overall yield. We believe that the presented efficient synthetic strategy would permit ready access to CPT-family alkaloids *via* the pivotal enantioselective cyanosilylation catalyzed by bifunctional organic catalysts.

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 from CaH_2, and AcOEt and petroleum ether for column chromatography (CC) were distilled before use. TLC: glass-backed silica gel *60* F_{254}

6) For an efficient synthesis of 2-amino-5-hydroxypropiophenone see [2].

plates. HPLC: *Shimadzu-LC-10AT* liquid chromatograph with an *Spd-10A* UV/VIS detector, working at 312 nm; *Chiralcel-OD-H* column (250 × 4.6 mm), elution with hexane/^{i}PrOH 70:30 at a flow rate of 0.5 ml/min. M.p.: *WRS-1B* digital melting-point apparatus; uncorrected. Optical rotations: *Jasco-P1020* digital polarimeter. ^{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. Mass spectra: *Waters-Quattro-Micromass* instrument; electrospray ionization (ESI) techniques; in *m*/*z*.

*2′,3′-Dihydro-6′-(hydroxymethyl)-7′-(1-oxopropyl)spiro[1,3-dioxolane-2,1′(5′*H*)-indolizin]-5′-one* (**3**). A soln. of $NaHCO_3$ (2.52 g, 30 mmol) in H_2O (20 ml) was added to the soln. of **2** (3.07 g, 10 mmol) in MeOH (60 ml) at r.t. (25°), and the mixture was stirred for 2 h. The solvent was evaporated and the residue neutralized to pH 7 with 10% aq. HCl soln. and then extracted with CH_2Cl_2 (3 × 20 ml). The combined org. phase was washed with brine (40 ml) and dried ($NaSO_4$). Evaporation of the solvent gave **3** (2.60 g, 93%) as a white solid, which was sufficiently pure for the subsequent reaction. M.p. 161.7–161.8° (dec.). ^{1}H-NMR ($CDCl_3$): 6.28 (*s*, =CH); 4.90 (*AB*, J = 12, CH_2OH); 4.09–4.21 (*m*, OCH_2CH_2O, CH_2CH_2N); 3.43 (br. *s*, OH); 2.42 (*t*, J = 8, CH_2CH$_2$N); 1.92–2.07 (*m*, MeCH_2), 0.86 (*t*, J = 8, *Me*CH$_2$). ESI-MS: 302 ([M + Na]$^+$).

*6′-{[[(*tert*-Butyl)dimethylsilyl]oxy}methyl}-2′,3′-dihydro-7′-(1-oxopropyl)spiro[1,3-dioxolane-2,1′(5′*H*)-indolizin]-5′-one* (**4**). A soln. of ^{t}BuMe$_2$SiCl (2.26 g, 15 mmol) in anh. CH_2Cl_2 (20 ml) was added dropwise to a mixture of **3** (2.80 g, 10 mmol), DMAP (0.28 g, 2.3 mmol), and 1*H*-imidazole (2.04 g, 30 mmol) in anh. CH_2Cl_2 (40 ml) at 0°. The mixture was stirred at r. t. (25°) for 36 h, and then quenched with H_2O (80 ml) and extracted with CH_2Cl_2 (2 × 50 ml). The combined org. layer was washed with brine (2 × 50 ml), dried ($MgSO_4$), and concentrated, and the residue purified by CC (CH_2Cl_2/MeOH 10:1): **4** (3.54 g, 90%). Colorless oil. ^{1}H-NMR ($CDCl_3$): 6.04 (*s*, CHCN); 4.75 (*s*, CH_2OSi); 4.08–4.14 (*m*, OCH_2CH_2O, CH_2CH_2N); 2.78 (*q*, J = 8, MeCH_2); 2.37 (*t*, J = 8, CH_2CH$_2$N); 1.13 (*t*, J = 8, *Me*CH$_2$); 0.87 (*s*, *Me*$_3$CSi); 0.07 (*s*, 2 *Me*Si). ^{13}C-NMR ($CDCl_3$): 205.97; 159.87; 149.90; 147.33; 127.45; 113.07; 97.62; 65.50; 58.68; 44.86; 36.19; 33.97; 25.94; 25.62; 18.53; 7.54; 5.63. ESI-MS: 416 ([M + Na]$^+$).

*(*α*R)-6′-{[[(*tert*-Butyl)dimethylsilyl]oxy}methyl]-*α*-ethyl-2′,3′-dihydro-5′-oxo-*α*-[(trimethylsilyl)oxy]-spiro[1,3-dioxolane-2,1′(5′*H*)-indolizine]-7′-acetonitrile* (**5**). Under Ar, a mixture of **4** (393 mg, 1 mmol), Me_3SiCN (0.40 ml, 300 mg, 3 mmol), and catalyst **7** (60 mg, 0.1 mmol) in anh. CH_2Cl_2 (5 ml) was stirred at −10° for 30 min. CF_3CH_2OH (0.11 ml, 150 mg, 1.5 mmol) was then added *via* syringe, and the mixture was continuously stirred at −10° for 80 h. After warming to r.t., the entire mixture was purified by flash CC (AcOEt/petroleum ether 1:1) to afford **5** (420 mg, 85%) as a pale-yellow oil. The product was not very stable on a chiral *OD-H* column; thus the enantiomer excess was determined at the tricyclic-lactone stage. ^{1}H-NMR ($CDCl_3$): 6.52 (*s*, =CH); 4.90, 5.05 (2*d*, J = 8, CH_2OSi); 4.09–4.18 (*m*, OCH_2CH_2O, CH_2CH_2N); 2.39 (*t*, J = 8, MeCH_2); 2.28–2.20 (*m*, CH_2CH$_2$N), 1.03 (*t*, J = 8, *Me*CH$_2$), 0.91 (*s*, *Me*$_3$CSi); 0.17 (*s*, 3 *Me*Si); 0.09 (*s*, 2 *Me*Si). ^{13}C-NMR ($CDCl_3$): 161.19; 150.88; 147.21; 127.51; 119.88; 113.30; 97.80; 75.75; 65.56; 65.52; 55.54; 45.06; 37.04; 33.80; 25.93; 25.70; 18.47; 8.50; 0.85; −5.34; −5.47. ESI-MS: 416 ([M + Na]$^+$).

*(4*S*)-4-Ethyl-7,8-dihydro-4-hydroxy-1*H*-pyrano[3,4-*f*]indolizine-3,6,10(4*H*)-trione* (**6**). A soln. of **5** (250 mg, 0.5 mmol) in anh. EtOH (5 ml) was treated with HCl(g) at 0° for 30 min. The mixture was heated under reflux for 3 h and then cooled to r.t. The solvent was evaporated, the residue diluted with CH_2Cl_2 (50 ml), the soln. washed with H_2O (2 × 50 ml) and brine (2 × 50 ml), dried ($NaSO_4$), and concentrated, and the residue purified by CC (CH_2Cl_2/MeOH 10:1): **6** (80 mg, 60%, 65% *ee*). Off-white solid. M.p. 183–185° (dec.) ([1e]: m.p. 176–177°). [α]$_D^{25}$ = +77.8 (c = 0.62, $CHCl_3$) ([1e]: [α]$_D^{20}$ = +120.6 (c = 0.62, $CHCl_3$)). ^{1}H-NMR ($CDCl_3$): 7.22 (*s*, =CH); 5.24, 5.68 (*AB*, J = 16, CH_2O); 4.34 (*t*, J = 8, CH_2N); 3.68 (*s*, OH); 2.97 (*t*, J = 8, COCH_2); 1.60–1.84 (*m*, MeCH_2), 0.98 (*t*, J = 8, *Me*CH$_2$). ESI-MS: 264 ([M + H]$^+$).

(*20*S)-*7-Ethyl-10-hydroxycamptothecin* (=*(4*S*)-4,11-Diethyl-4,9-dihydroxy-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione* (= SN 38); **1f**). A mixture of 1-(2-amino-5-hydroxyphenyl)propan-1-one (364 mg, 2.2 mmol), **6** (526 mg, 2 mmol), and I_2 (50.8 mg, 0.1 mmol) in anh. DMF (10 ml) under Ar was stirred at 80° for 8 h. The mixture was cooled to r.t. and then poured into ice/H_2O (50 ml). The precipitate was filtered and then recrystallized from EtOH/AcOH 3:7: **1f** (590 mg, 75%). Yellow solid. M.p. 218–220° (dec.) ([11]: m.p. 215–217° (dec.)). [α]$_D^{25}$ = +17.8 (c = 0.50, $CHCl_3$/MeOH

4:1); ([11]: $[\alpha]_D^{20} = +29.3$ ($c = 0.45$, $CHCl_3$/MeOH 4:1)). ^{1}H-NMR ((D_6)DMSO): 10.29 (*s*, H−C(9)); 8.00 (*d*, $J = 8$, H−C(11)); 7.38 (*d*, $J = 8$, H−C(12)); 7.37 (*s*, OH−C(10)); 7.23 (*s*, OH−C(20)); 6.46 (*s*, H−C(14)); 5.40 (*s*, CH_2(5)); 5.23 (*s*, CH_2(17)); 3.06 (*q*, $J = 8$, MeCH_2−C(7)); 1.81 – 1.88 (*m*, MeCH_2−C(20)); 1.28 (*t*, $J = 8$, *Me*CH_2−C(7)); 0.87 (*t*, $J = 8$, *Me*CH_2−C(20)). ESI-MS: 393 ($[M+H]^+$).

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