ChemPubSoc Europe

DOI: 10.1002/chem.201303633

CHEMISTRY
A European Journal
Full Paper

Asymmetric Synthesis

Asymmetric α-Hydroxylation of a Lactone with Vinylogous Pyridone by Using a Guanidine–Urea Bifunctional Organocatalyst: Catalytic Enantioselective Synthesis of a Key Intermediate for (20*S*)-Camptothecin Analogues

Tatsuya Watanabe, Minami Odagi, Kota Furukori, and Kazuo Nagasawa*[a]

Abstract: We have developed a catalytic asymmetric synthesis of (*S*)-4-ethyl-6,6-(ethylenedioxy)-7,8-dihydro-4-hydroxy-1*H*-pyrano[3,4-*f*]indolizine-3,10(4*H*)dione (**5a**), a synthetic intermediate for (20*S*)-camptothecin analogues. A key step in this synthesis is an asymmetric α-hydroxylation of a lactone with a vinylogous pyridone structure (**8a**) by using a guanidine–urea bifunctional organocatalyst. The present oxidation was successfully applied to the synthesis of C20-modified derivatives of (+)-C20-desethylbenzylcamptothecin (**13**).

Introduction

Camptothecin (CPT **1**), a pentacyclic alkaloid, was isolated from *Camptotheca acuminata* by Wall and co-workers in 1966 (Figure 1).[1] CPT (**1**) shows significant antitumor activity

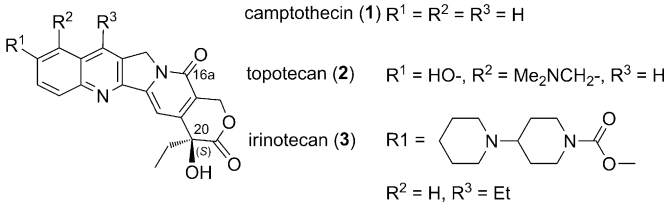


Figure 1. Structures of camptothecin (**1**) and its water-soluble analogues **2** and **3**.

through inhibition of topoisomerase I (Topo I),[2] which is overexpressed in some types of solid tumors. Early clinical trials of **1** carried out in the mid 1970s achieved partial success, but were subsequently discontinued due to serious toxicity concerns.[3] Since then, extensive structure–activity relationship studies have been conducted, especially focusing on improving the solubility of **1** in water. Currently, two camptothecin derivatives, topotecan (**2**)[4] and irinotecan (**3**),[5] are in clinical use for treatment of solid tumors.

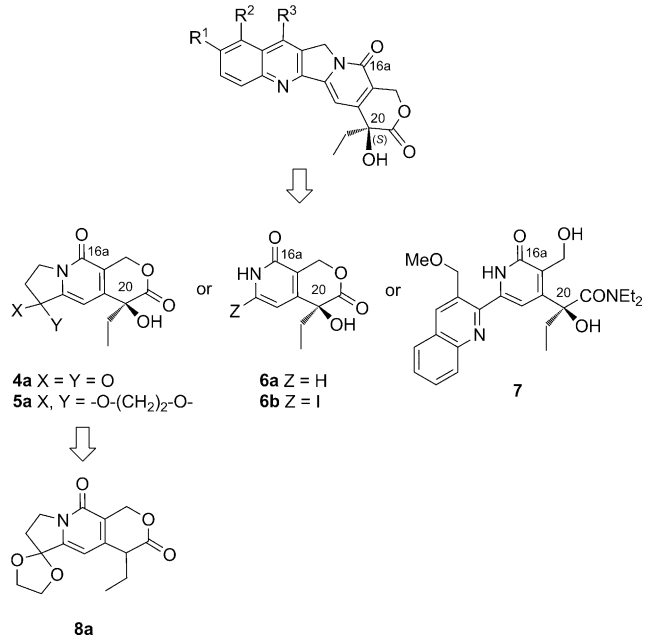
In the synthesis of **1** and its analogues, construction of the stereogenic center at C20 is an important issue,[6,7] and synthetic studies of the key intermediates **4a**,[8,10d,12] **6**,[9,10a–c,11] and **7**[13] have mainly employed one of four approaches, that is, 1) chiral auxiliary-mediated alkylation,[8,9] 2) asymmetric dihydroxylation,[10] 3) asymmetric cyanosilylation,[11] 4) chemical and/or enzymatic optical resolutions,[12] and 5) enzymatic desymmetrization.[13] The intermediates **4a** and **6** have been obtained with high selectivity. However, there are some disadvantages to these approaches, such as the need for stoichiometric usage of a chiral auxiliary, use of highly toxic reagents, or a requirement for low temperature. Moreover, the undesired isomer is wasted in the case of the optical resolution methods. Ciufolini and co-workers have developed a very efficient strategy for the synthesis of the key intermediate **7** by enzymatic desymmetrization.[13] Recently, a more straightforward approach to direct α-hydroxylation of **8a** with chiral oxaziridine in the presence of potassium hexamethyl disilazide (KHMDS) has been investigated by Chen and co-workers (Scheme 1),[7b] and the hydroxylation product **4a** was obtained in 82% yield with 72% *ee*.

We have recently developed an asymmetric α-hydroxylation of β-ketoesters by using a guanidine–urea bifunctional organocatalyst **10a** in the presence of cumene hydroperoxide (CHP) and K_2CO_3.[14] In this reaction, guanidine and urea in the catalyst are suggested to interact with β-ketoester and oxidant, respectively (Scheme 2). The chiral spacer in the catalyst serves to control the transition state for the asymmetric induction, and is believed to accelerate the reaction by a synergistic proximity effect.[15]

Based upon the plausible interacting model shown in Scheme 2, we envisaged applying this catalytic asymmetric oxidation to the synthesis of the key intermediate **5** for camptothecins. Thus, α-hydroxylation of **8** was planned in the presence of guanidine–urea bifunctional organocatalyst **10**. Com-

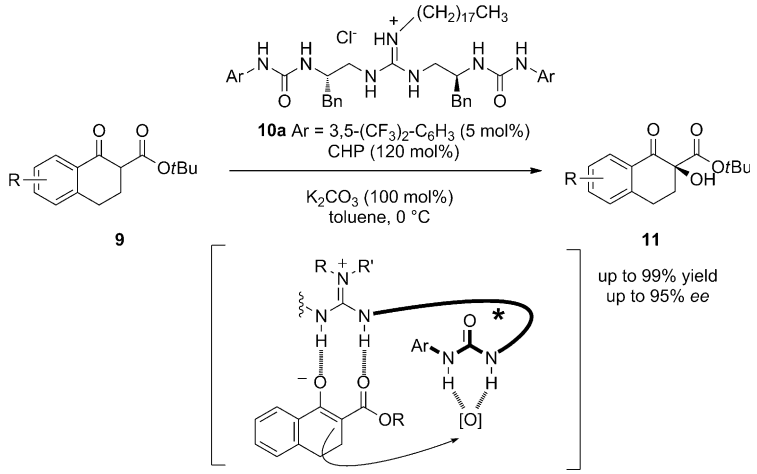
[a] *T. Watanabe, M. Odagi, K. Furukori, Prof. Dr. K. Nagasawa*
Department of Biotechnology and Life Science
Tokyo University of Agriculture and Technology
2-24-16 Naka-cho, Koganei
Tokyo 184-8588 (Japan)
Fax: (+81) 42-388-7295
E-mail: knaga@cc.tuat.ac.jp

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201303633.

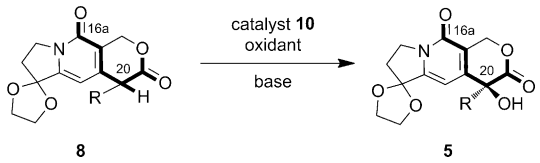


Scheme 1. Retrosynthetic approach to camptothecin (**1**) and its analogues.

pound **8** does not have a simple 1,3-dicarbonyl moiety; instead, C20 in **8** is regarded as a vinylogous position to the carbonyl group at C16a in the 2-pyridone structure (Scheme 3). Therefore, we planned to generate an enolate efficiently from **8** by using an appropriate base to promote α-hydroxylation in the presence of a guanidine–urea bifunctional organocatalyst **10** and an oxidant. Here, we described enantioselective organocatalytic α-hydroxylation of **8a**. We also examined the substrate scope of the oxidation by using a variety of C20 substituents in **8**. These results will be helpful for the synthesis of C20-modified camptothecin derivatives.

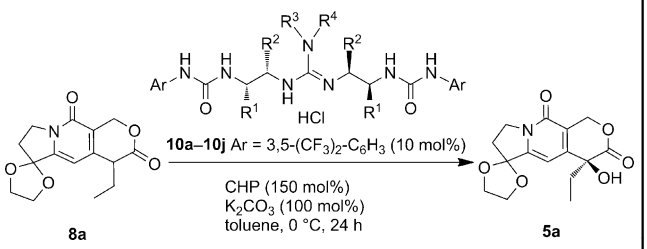


Scheme 2. Asymmetric α-hydroxylation of β-ketoesters catalyzed by guanidine–urea bifunctional organocatalyst **10a**, and a plausible interacting model of the reaction.



Scheme 3. Asymmetric α-hydroxylation of a lactone with vinylogous pyridine **8** for the synthesis of **5**, a key intermediate of camptothecin (**1**) and its derivatives, by using guanidine–urea bifunctional organocatalyst **10**.

Table 1. Asymmetric α-hydroxylation of lactone **8a** by using guanidine–urea bifunctional organocatalysts **10a–j**.[a]



Entry	Cat.	R^1	R^2	R^3	R^4	5a Yield [%]	5a *ee* [%][b]
1	**10a**	Bn	H	H	$(CH_2)_{17}Me$	99	22
2	**10b**	Me	H	H	$(CH_2)_{17}Me$	70	52
3	**10c**	*i*Pr	H	H	$(CH_2)_{17}Me$	89	49
4	**10d**	Ph	H	H	$(CH_2)_{17}Me$	93	20
5	**10e**	*i*Bu	H	H	$(CH_2)_{17}Me$	97	37
6	**10f**	H	Me	H	$(CH_2)_{17}Me$	95	10
7	**10g**	Me	H	Et	Et	94	65
8	**10h**	Me	H		$-(CH_2)_3-$	99	66
9	**10i**	Me	H		$-(CH_2)_4-$	97	76
10	**10j**	Me	H		$-(CH_2)_5-$	92	56

[a] Reactions were performed with **8a** (0.1 mmol), CHP (0.15 mmol), K_2CO_3 (0.1 mmol), and catalyst (0.01 mmol) in toluene at 0 °C for 24 h. [b] Racemic **5a** and (*S*)-**5a** were prepared according to ref. [8b] and [8c], respectively. The enantiomeric excess and the absolute stereochemistry were determined by chiral HPLC analysis.

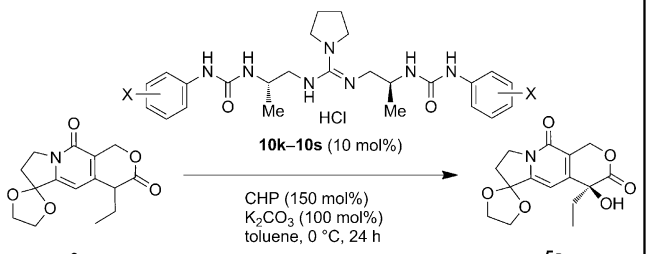
Results and Discussion

At the outset, we investigated α-hydroxylation of **8a** with cumene hydroperoxide (CHP)[16] and K_2CO_3 in toluene in the presence of guanidine–urea bifunctional organocatalyst **10a**[15f] (10 mol%). In this reaction, hydroxylation proceeded efficiently at 0 °C, and compound **5a** was obtained in 99% yield with 22% *ee* (Table 1, entry 1). Although the selectivity was low, the catalytic system was effective for the oxidation reaction of **8a**, so we next carried out a structure–activity relationship study of the catalyst by varying the R^1 and R^2 groups on the chiral spacer in **10a** (Table 1, entries 2–6). In the case of catalysts **10b**[15f] (R^1 = Me) and **10c**[15f] (R^1 = *i*Pr), compound **5a** was obtained with 52 and 49% *ee*, respectively (entries 2 and 3). On the other hand, the reaction with catalysts **10d** bearing an aromatic group (R^1 = Ph) and **10e** bearing a bulky substituent (R^1 = *i*Bu) resulted in lower enantioselectivity (entries 4 and 5). Interestingly, the catalyst **10f**, with a methyl group at another position in the chiral spacer, gave **5a** in good yield, but the enantioselectivity was considerably reduced compared to that with catalyst **10b** (entry 6 vs. 2). Next, we examined the effects of substituents on the guanidine group (R^3 and R^4) of the catalysts (entries 7–10). Changing

the octadecylamino group to a disubstituted diethylamino **10g** or an azetidino group **10h** increased the enantioselectivity to 65 and 66% *ee*, respectively, with high yield (entries 7 and 8). Furthermore, catalyst **10i** bearing a pyrrolidine substituent on guanidine gave **5a** in 97% yield with 76% *ee* (entry 9). On the other hand, piperidine-substituted derivative **10j** gave decreased enantioselectivity (56% *ee*, entry 10).

We further optimized the catalyst structure based upon the catalyst **10i**, especially focusing on the aromatic group attached to the urea moiety (Table 2). In the case of phenyl urea **10k**, the enantioselectivity decreased slightly to 70% *ee* (Table 2, entry 1 vs. Table 1, entry 9). On the other hand, 3,5-di-F-substituted **10l** showed a similar level of selectivity to catalyst **10i** (Table 2, entry 2). Catalysts bearing a CF_3 group at the 2- or 3-position on the phenyl group of urea **10m** and **10n** also showed comparable enantioselectivity to catalyst **10i** (entries 3 and 4). Interestingly, 4-CF_3-substituted phenyl urea **10o** gave increased selectivity, and **5a** was obtained in 95% yield with 84% *ee* (entry 5). Since substitution at the 4-position on the aromatic ring seemed to be effective for obtaining high enantioselectivity, substituent effects at this position were further explored. Catalysts **10p** (4-F), **10q** (4-OCF_3), and **10r** (4-NO_2) showed a similar level of enantioselectivity to catalyst **10o** (entries 6–8). On the other hand, the reaction with catalyst **10s** (4-OMe) resulted in lower enantioselectivity (entry 9). The catalyst loading was examined with **10o**, and it was found that loading could be reduced to 5 mol% without affecting the yield or selectivity (entry 10). Furthermore, enantiomeric purity was increased to 93% *ee* by a single recrystallization from ethanol (entry 10).

Table 2. Asymmetric α-hydroxylation of lactone **8a** by using guanidine–urea bifunctional organocatalysts **10k**–**s**.[a]

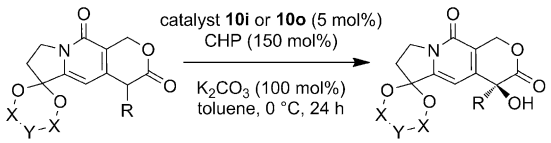


8a **5a**

Entry	Cat.	X	Yield [%]	*ee* [%][b]
1	**10k**	H	93	70
2	**10l**	3,5-di-F	86	76
3	**10m**	2-CF_3	89	75
4	**10n**	3-CF_3	93	78
5	**10o**	4-CF_3	95	84
6	**10p**	4-F	99	82
7	**10q**	4-OCF_3	85	83
8	**10r**	4-NO_2	96	82
9	**10s**	4-OMe	70	78
10	**10o**[c]	4-CF_3	93	84, 93[d]

[a] Reactions were performed with **8a** (0.1 mmol), CHP (0.15 mmol), K_2CO_3 (0.1 mmol), and catalyst (0.01 mmol) in toluene at 0 °C for 24 h. [b] Racemic **5a** and (*S*)-**5a** were prepared according to ref. [8b] and [8c], respectively. The enantiomeric excess and the absolute stereochemistry were determined by chiral HPLC analysis. [c] Reaction was carried out with 5 mol% of catalyst **10o**. [d] Enantiomeric purity was increased to 93% *ee* by a single recrystallization from ethanol.

Table 3. Asymmetric α-hydroxylation of lactones **8b**–**e** by using a guanidine–urea bifunctional organocatalyst **10i** or **10o**.[a]



8b -X-Y-X- = -$(CH_2)_2$-, R = Me
8c -X-Y-X- = -$(CH_2)_2$-, R = *n*Bu
8d -X-Y-X- = -$(CH_2)_2$-, R = $(CH_2)_2$Ph
8e -X-Y-X- = -$CH_2C(Me)_2CH_2$-, R = Bn

5b -X-Y-X- = -$(CH_2)_2$-, R = Me
5c -X-Y-X- = -$(CH_2)_2$-, R = *n*Bu
5d -X-Y-X- = -$(CH_2)_2$-, R = $(CH_2)_2$Ph
5e -X-Y-X- = -$CH_2C(Me)_2CH_2$-, R = Bn

Entry	Substrate	Cat.	Product[b]	Yield [%]	ee [%][c,d]
1	**8b**	**10i**	**5b**	99	75
2	**8c**	**10o**	**5c**	95	82
3	**8d**	**10o**	**5d**	90	82
4	**8e**[e]	**10i**	**5e**	99	80, 90[f]

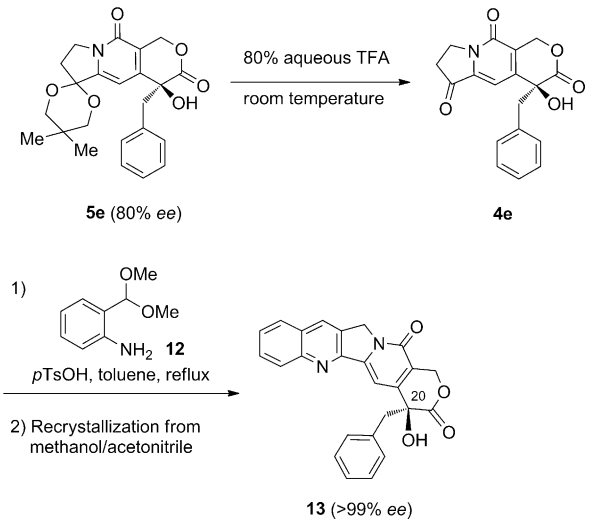
[a] Reactions were performed with **8** (0.1 mmol), CHP (0.15 mmol), K_2CO_3 (0.1 mmol), and catalyst (0.005 mmol) in toluene at 0 °C for 24 h. [b] Racemic α-hydroxy lactones **5b**–**e** for HPLC analysis were derived from lactones **8b**–**e** by reaction with NaHMDS and (±)-*N*-tosyl-phenyloxaziridine[19] in THF. [c] The enantiomeric excess was determined by chiral HPLC analysis. [d] Absolute stereochemistries were deduced from the results of oxidation of **5a**. [e] Oxidation did not proceed in the case of **8f** with ethylene dioxide-derived acetal at C2 because of its insolubility.[20] Thus, we examined the reaction with **8e** bearing neopentyl glycol-derived acetal. [f] Enantiomeric purity was increased into 90% *ee* by a single recrystallization from ethanol.

Next, a series of lactones **8b**–**e**[17] bearing a methyl, *n*-butyl, 1-phenylethyl, or benzyl group as R, respectively, were tested by using the guanidine–urea catalyst **10i** or **10o**.[18] In these reactions, the corresponding products **5b**–**e** were obtained in high yields with good *ee* (Table 3, entries 1–4).

The cytotoxicity of **1** is modified by variation of the substituent at C20,[21] thus product **5e** was applied to a synthesis of (+)-C20-desethylbenzyl camptothecin (**13**)[22,23] (Scheme 4). Deprotection of the acetal in **5e** (80% *ee*) with 80% trifluoroacetic acid (TFA) afforded ketone **5e**. This ketone was subjected to the Friedlander reaction with aniline **12**[24] in the presence of *p*-toluenesulfonic acid to give (+)-C20-desethylbenzyl camptothecin (**13**). Optically pure compound (+)-**13** was isolated in 16% yield from **5e** by means of a single recrystallization from methanol/acetonitrile.

Elucidation of a catalytic reaction mechanism based upon structure–activity relationship studies

To gain insight into the cooperative roles of the guanidine and urea groups and the chiral spacer in the catalysts **10**, we performed the following control experiments using as catalysts the carbamate **14**[25] (lacking urea), triurea **15**[26] (lacking guanidine), and unsymmetrical **16**[26] (lacking C_2 symmetry) bearing a monomethyl chiral spacer under the conditions used in Table 2, entry 5 (Table 4). In the case of catalyst **14**, no reaction took place, but addition of urea **17**[27] (10 mol%) under catalytic conditions effectively promoted the reaction, and **5a** was



Scheme 4. Synthesis of (+)-C20-desethylbenzyl camptothecin (**13**).[24]

obtained in 85% yield, although its enantioselectivity was low (entries 1 and 2). Triurea **15** only showed low catalytic activity, but the yield of **5a** was increased to 64% by addition of 10 mol% of tetramethyl guanidine (**18**), although enantioselectivity was low in both cases (entries 3 and 4). In the case of unsymmetrical catalyst **16**, the product **5a** was obtained with high yield, but enantioselectivity was drastically reduced to 20% *ee* (entry 5 versus 2 in Table 1). Thus, these results clearly show that both the guanidine center as a base site and the H-bond sites of the urea moiety are mandatory for promoting the reaction effectively. Moreover, C_2-symmetrical structure was crucial to achieve high enantioselectivity in the α-hydroxylation of lactones **8**.

Based upon those findings together with the absolute stereochemistry of (*S*)-**5a** at C20, a possible transition state for this reaction in the presence of catalyst **10** was proposed to account for the enantioselectivity, as shown in Figure 2. Substrate **8a** coordinates with guanidine as an enolate form, while at the same time, the urea part of the catalyst interacts with CHP, which is activated via a double hydrogen-bonding interaction. Then nucleophilic attack of the enolate takes place on CHP from the preferential transition state TS-1, which avoids the steric repulsion between the ethyl group in **8a** and the urea moiety in the catalyst, resulting in the formation of (*S*)-**5a**.

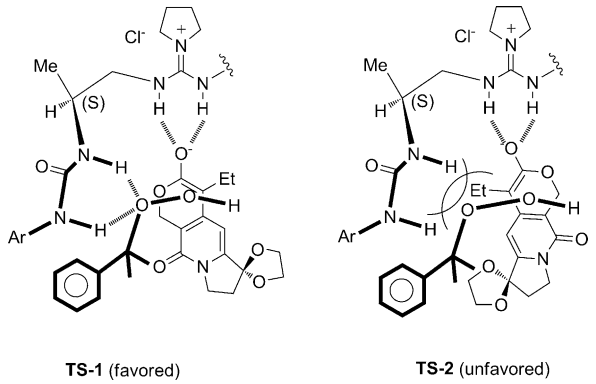
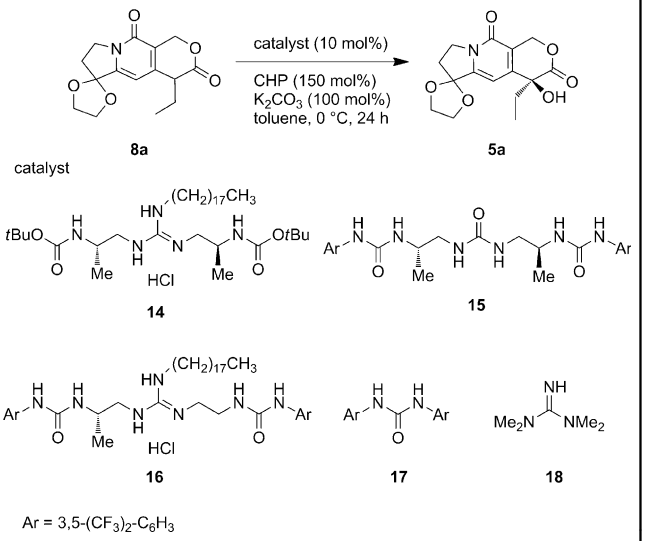


Figure 2. Plausible transition state of the α-hydroxylation catalyzed by **10**.

Table 4. Cooperative effects of guanidine and urea and the chiral spacer in α-hydroxylation catalysts.[a]



Entry	Cat.	Additive (equiv)	5a Yield [%]	5a *ee* [%][b]	5a *R* or *S*
1	**14**	–	trace	–	–
2	**14**	**17** (0.1)	85	8	*R*
3	**15**	–	25	7	*S*
4	**15**	**18** (0.1)	64	5	*S*
5	**16**	–	92	20	*S*

[a] Reactions were performed with **8a** (0.1 mmol), CHP (0.15 mmol), K_2CO_3 (0.1 mmol), and catalyst (0.01 mmol) in toluene at 0 °C for 24 h. [b] The enantiomeric excess and the absolute stereochemistry were determined by chiral HPLC analysis.

Conclusion

In summary, we have developed a catalytic asymmetric α-hydroxylation of a vinylogous-type lactone **8a** utilizing guanidine–urea bifunctional organocatalyst **10** for synthesis of **5a**, which is a key synthetic intermediate of (20*S*)-camptothecin and its analogues. The functional groups of guanidine and urea and the chiral spacer in **10** act cooperatively to give **5a** in high yield (up to 99%) with high enantioselectivity (up to 84% *ee*). This new catalytic oxidation was efficiently applied to the synthesis of C20-modified camptothecin analogue (+)-**13**.

Experimental Section

General remarks

Flash chromatography was performed using silica gel 60 (spherical, particle size 0.040–0.100 mm. Kanto Co., Japan) or NH silica gel (spherical, particle size 0.06 mm, Fuji Silysia Chemical, Japan). Optical rotations were measured on a JACO P-2200 polarimeter. ^1H and ^{13}C NMR spectra were recorded on AL300 (JEOL), ECX400 (JEOL), JNM500 (JEOL), or AVANCE400 (Bruker) instruments. Chemical shifts in [D]chloroform, [D_4]MeOH, or [D_6]dimethylsulfoxide were reported in the scale relative to [D]chloroform ($\delta = 7.26$ ppm), [D_4]MeOH

($\delta = 3.30$ ppm), and [D_6]dimethylsulfoxide ($\delta = 2.50$ ppm) for ^{1}H NMR spectroscopy, respectively. For ^{13}C NMR spectra, chemical shifts were reported in the scale relative to [D]chloroform ($\delta =$ 77.0 ppm), [D_4]MeOH ($\delta = 49.0$ ppm), or [D_6]dimethylsulfoxide ($\delta =$ 39.5 ppm) as internal references, respectively. Mass spectra were recorded on a JMS-T100LC (JEOL) spectrometer. Melting points were measured on a Büchi model B-545 instrument without correction. Elemental analyses were performed by using a Perkin–Elmer 2400 CHN-Analyzer and Yokogawa IC7000S ion chromatograph (oxygen flask method).

General procedure for catalytic asymmetric α-hydroxylation of pyranoindolizine derivatives 8 by using guanidine–urea bifunctional organocatalysts 10

A test tube equipped with a magnetic stirring bar was charged with catalyst **10** (0.01 mmol), pyranoindolizine derivative **8** (0.1 mmol), K_2CO_3 (0.1 mmol), and toluene (1.0 mL) at room temperature. The mixture was cooled to 0 °C and stirred for 10 min. Then, cumene hydroperoxide (0.15 mmol) was added to it, and the whole was stirred at 0 °C for 24 h. The reaction was quenched by addition of $Na_2S_2O_3$ solution (10%, 2 mL) and acetic acid (0.2 mL), and the mixture was vigorously stirred at room temperature for 1 h. The organic layer was separated and the aqueous layer was extracted three times with $CHCl_3$. The combined organic solution was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate 1:1 to $CHCl_3/CH_3OH$ 100:1) to give the product **6**. The enantiomeric excess and the absolute configuration were determined by HPLC analysis of the product by using a chiral column (DAICEL Chiralpak IA) with *n*-hexane/ethanol as the eluent.

α-Hydroxy lactone 5a: For details of the spectral data of α-hydroxy lactone **5a**, see the ref. [8b]. Enantiomeric excess of **5a** was determined by chiral HPLC analysis: DAICEL Chiralpak IA column (250×4.6 mm), *n*-hexane/ethanol 60:40, flow rate 1 mL min^{-1}, $\lambda = 220$ nm, $\tau_1 = 18.93$ (major), $\tau_2 = 24.92$ (minor).

α-Hydroxy lactone 5b: 99% yield; $[\alpha]_D^{25} = +66.6$ ($c = 1.0$ in $CHCl_3/CH_3OH$ 1:1);^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.27$ (d, $J = 7.3$ Hz, 3H), 2.4 (t, $J = 6.9$ Hz, 2H), 3.5 (q, $J = 6.9$ Hz, 1H), 4.10–4.21 (m, 6H), 5.24 (d, $J = 15.6$ Hz, 1H), 5.43 (d, $J = 15.6$ Hz, 1H), 6.19 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 25.9$, 33.9, 44.8, 65.5, 65.8, 66.0, 95.8, 113.0, 118.1, 149.8, 150.2, 157.4, 174.5 ppm; HRMS (ESI): calcd for $C_{14}H_{15}N_1O_6Na$: 316.0797 $[M+Na]^+$; found: 316.0784; enantiomeric excess of **5b** was determined to be 75% *ee* by chiral HPLC analysis: DAICEL Chiralpak IA column (250×4.6 mm), *n*-hexane/2-propanol 70:30, flow rate: 1 mL min^{-1}, $\lambda = 220$ nm, $\tau_1 = 20.20$ (major), $\tau_2 = 15.91$ (minor).

α-Hydroxy lactone 5c: 95% yield; $[\alpha]_D^{25} = +75.9$ ($c = 0.91$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.87$ (t, $J = 7.6$ Hz, 3H), 1.22–1.39 (m, 3H), 1.67–1.81 (m, 3H), 2.42 (t, $J = 6.9$ Hz, 2H), 3.74 (s, 1H), 4.07–4.23 (m, 6H), 5.17 (d, $J = 16$ Hz, 1H), 5.61 (d, $J = 16$ Hz, 1H), 6.57 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.7$, 22.3, 25.2, 33.8, 37.8, 44.7, 65.4, 65.5, 66.1, 72.2, 96.6, 112.9, 118.2, 149.2, 150.0, 157.4, 173.7 ppm; HRMS (ESI, $[M+Na]^+$): calcd for $C_{17}H_{21}NO_6Na$: 358.1267; found: 358.1222; enantiomeric excess of **5c** was determined to be 82% *ee* by chiral HPLC analysis: DAICEL Chiralpak IA column (250×4.6 mm), *n*-hexane/2-propanol 70:30, flow rate: 1 mL min^{-1}, $\lambda = 220$ nm, $\tau_1 = 26.51$ (major), $\tau_2 = 17.35$ (minor).

α-Hydroxy lactone 5d: 90% yield; $[\alpha]_D^{25} = +13.3$ ($c = 0.92$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.96$–2.12 (m, 2H), 2.42 (t, $J =$ 6.9 Hz, 2H), 2.66–2.76 (m, 2H), 3.87 (s, 1H), 4.08–4.25 (m, 6H), 5.19 (d, $J = 16$ Hz, 1H), 5.64 (d, $J = 16$ Hz, 1H), 6.62 (s, 1H), 7.12 (d, $J =$ 6.9 Hz, 2H), 7.18 (t, $J = 7.5$ Hz, 1H), 7.25 ppm (d, $J = 8.6$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 29.5$, 33.8, 39.6, 44.8, 65.5, 65.6, 66.2, 72.1, 96.6, 112.9, 118.3, 126.2, 128.2, 128.4, 140.0, 149.4, 149.6, 157.4, 173.5 ppm; HRMS (ESI): calcd for $C_{21}H_{21}NO_6Na$: 406.1266 $[M+Na]^+$; found: 406.1222; enantiomeric excess of **5d** was determined to be 82% *ee* by chiral HPLC analysis: DAICEL Chiralpak IA column (250×4.6 mm), *n*-hexane/2-propanol 70:30, flow rate: 1 mL min^{-1}, $\lambda = 220$ nm, $\tau_1 = 32.06$ (major), $\tau_2 = 25.84$ (minor).

α-Hydroxy lactone 5e: 99% yield; $[\alpha]_D^{25} = +26.7$ ($c = 0.55$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.90$ (s, 3H), 1.26 (s, 3H), 2.48–2.58 (m, 2H), 3.09 (q, $J = 13.2$, 30.9 Hz, 2H), 3.65 (s, 2H), 3.67 (s, 2H), 4.09–4.19 (m, 2H), 4.63 (d, $J = 16$ Hz, 1H), 5.46 (d, $J = 16$ Hz, 1H), 6.72 (s, 1H), 7.06–7.08 (m, 2H), 7.26–7.27 ppm (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 22.1$, 22.5, 29.8, 30.3, 45.4, 46.0, 66.2, 72.2, 72.3, 72.8, 97.6, 105.0, 119.2, 127.6, 128.2, 130.1, 132.8, 148.2, 149.2, 157.0, 172.9 ppm; HRMS (ESI, $[M+Na]^+$): calcd for $C_{23}H_{25}NO_6Na$: 434.1580; found: 434.1561; enantiomeric excess of **5e** was determined to be 80% *ee* by chiral HPLC analysis: DAICEL Chiralpak IA column (250×4.6 mm), *n*-hexane/ethanol 60:40; flow rate: 1 mL min^{-1}, $\lambda = 220$ nm, $\tau_1 = 19.52$ (major), $\tau_2 = 11.60$ (minor).

Synthesis of guanidine–urea bifunctional organocatalysts (10d–s)

Compounds **10d–s** were synthesized according to the known procedure[15f,25] with minor modifications. See the Supporting Information for details.

Compound 10d: $[\alpha]_D^{29} = +39.4$ ($c = 1.2$ in CH_3OH); ^{1}H NMR (400 MHz, CD_3OD): $\delta = 0.89$ (t, $J = 6.9$ Hz, 3H), 1.13–1.40 (m, 32H), 1.52–1.67 (m, 2H), 3.09–3.50 (m, 4H), 4.91–4.98 (m, 2H), 7.30–7.56 (m, 12H), 8.00 ppm (s, 4H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 14.4$, 23.7, 27.9, 29.8, 30.3, 30.5, 30.56, 30.58, 30.66, 30.72, 30.75, 30.78, 33.1, 43.3, 48.5, 55.2, 115.9 (br), 119.1 (br), 124.8 (q, $J_{C-F} =$ 272.0 Hz), 128.2, 129.5, 130.2, 133.3 (q, $J_{C-F} = 33.1$ Hz), 140.2, 143.0, 156.5, 157.5 ppm; HRMS (ESI, $[M+H]^+$): calcd for $C_{53}H_{66}F_{12}N_7O_2$: 1060.5086; found: 1060.5097.

Compound 10e: $[\alpha]_D^{27} = +1.7$ ($c = 1.5$ in CH_3OH); ^{1}H NMR (400 MHz, CD_3OD): $\delta = 0.89$ (t, $J = 6.7$ Hz, 3H), 0.92 (d, $J = 6.2$ Hz, 6H), 0.98 (d, $J = 6.7$ Hz, 6H), 1.10–1.37 (m, 30H), 1.40–1.58 (m, 4H), 1.58–1.71 (m, 2H), 1.72–1.85 (m, 2H), 3.21 (t, $J = 7.2$ Hz, 2H), 3.24–3.34 (m, 4H), 3.9 (br, 2H), 7.5 (s, 2H), 8.04 ppm (s, 4H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 14.6$, 22.1, 23.9, 26.2, 28.0, 29.9, 30.3, 30.59, 30.64, 30.66, 30.74, 30.80, 30.82, 30.87, 30.90, 33.2, 42.5, 43.2, 48.6, 115.9 (br), 119.2 (br), 124.9 (q, $J_{C-F} = 272.0$ Hz), 133.4 (q, $J_{C-F} =$ 33.1 Hz), 143.3, 156.5, 158.2 ppm; HRMS (ESI): calcd for $C_{49}H_{74}F_{12}N_7O_2$: 1020.5712 $[M+H]^+$; found: 1020.5738.

Compound 10f: $[\alpha]_D^{30} = +39.2$ ($c = 1.2$ in CH_3OH); ^{1}H NMR (400 MHz, CD_3OD): $\delta = 0.89$ (t, $J = 6.9$ Hz, 3H), 1.14–1.32 (m, 30H), 1.35 (d, $J = 6.7$ Hz, 6H), 1.60–1.73 (m, 2H), 3.10–3.31 (m, 4H), 3.35–3.48 (m, 2H), 3.73–3.84 (m, 2H), 7.49 (s, 2H), 8.04 ppm (s, 4H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 14.6$, 18.4, 23.9, 28.0, 29.8, 30.3, 30.6, 30.66, 30.68, 30.76, 30.84, 30.88, 30.91, 33.2, 43.3, 46.7, 50.0, 115.9 (br), 119.2 (br), 125.0 (q, $J_{C-F} = 271$ Hz), 133.3 (q, $J_{C-F} = 33$ Hz), 143.3, 155.5, 158.5 ppm; HRMS (ESI): calcd for $C_{43}H_{62}F_{12}N_7O_2$: 936.4773 $[M+H]^+$; found: 936.4737.

Compound 10g: $[\alpha]_D^{27} = -42.4$ ($c = 1.3$ in CH_3OH); ^{1}H NMR (400 MHz, CD_3OD): $\delta = 1.18$ (t, $J = 6.9$ Hz, 6H), 1.26 (d, $J = 7.2$ Hz, 6H), 3.26–3.34 (m, 2H), 3.35–3.49 (m, 6H), 4.04–4.15 (m, 2H), 7.47 (s, 2H), 8.02 (s, 4H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 12.9$, 18.7, 44.3, 47.3, 52.0, 115.8 (br), 119.1 (br), 124.8 (q, $J_{C-F} = 272$ Hz), 133.2 (q, $J_{C-F} = 32$ Hz), 143.2, 157.6, 160.7; HRMS (ESI): calcd for $C_{29}H_{34}F_{12}N_7O_2$: 740.2582 $[M+H]^+$; found: 740.2597.

Compound 10h: $[\alpha]_D^{29} = -22.2$ ($c = 1.3$ in CH_3OH); ^1H NMR (400 MHz, CD_3OD): $\delta = 1.27$ (d, $J = 6.7$ Hz, 6H), 2.32–2.44 (m, 2H), 3.23–3.35 (m, 4H), 3.96–4.09 (m, 2H), 4.22–4.37 (m, 4H), 7.48 (s, 2H), 7.99 ppm (s, 4H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 16.9$, 18.4, 47.1, 50.0, 54.2, 115.9 (br), 119.2 (br), 124.9 (q, $J_{C-F} = 271.9$ Hz), 133.3 (q, $J_{C-F} = 33.3$ Hz), 143.3, 157.77, 157.82, 163.3, 163.7 ppm; HRMS (ESI): calcd for $C_{28}H_{30}F_{12}N_7O_2$: 724.2269 $[M+H]^+$; found: 724.2257.

Compound 10i: $[\alpha]_D^{29} = -34.6$ ($c = 1.1$ in CH_3OH); ^1H NMR (400 MHz, CD_3OD): $\delta = 1.26$ (d, $J = 6.7$ Hz, 6H), 1.83–2.03 (m, 4H), 3.26–3.37 (m, 2H), 3.42 (dd, $J = 4.9$, 13 Hz, 2H), 3.43–3.58 (m, 4H), 3.98–4.14 (m, 2H), 7.49 (s, 2H), 8 ppm (s, 4H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 18.6$, 26.3, 47.3, 50.3, 51.5, 115.8 (br), 119.1 (br), 124.9 (q, $J_{C-F} = 271.7$ Hz), 133.2 (q, $J_{C-F} = 33.1$ Hz), 143.2, 157.6, 157.9 ppm; HRMS (ESI): calcd for $C_{29}H_{32}F_{12}N_7O_2$: 738.2426 $[M+H]^+$; found: 738.2401.

Compound 10j: $[\alpha]_D^{29} = -40.5$ ($c = 1.1$ in CH_3OH); ^1H NMR (400 MHz, CD_3OD): $\delta = 1.25$ (d, $J = 7.2$ Hz, 6H), 1.64 (m, 6H), 3.25–3.39 (m, 6H), 3.42 (dd, $J = 4.3$, 13 Hz, 2H), 4.03–4.15 (m, 2H), 7.48 (s, 2H), 8.01 ppm (s, 4H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 18.8$, 25.0, 26.7, 47.3, 50.5, 51.5, 115.8 (br), 119.2 (br), 125.0 (q, $J_{C-F} = 271.5$ Hz), 133.3 (q, $J_{C-F} = 33.3$ Hz), 143.3, 157.5, 161.0 ppm; HRMS (ESI): calcd for $C_{30}H_{34}F_{12}N_7O_2$: 752.2582 $[M+H]^+$; found: 752.2594.

Compound 10k: $[\alpha]_D^{27} = -50.6$ ($c = 1.2$, CH_3OH); ^1H NMR (400 MHz, CD_3OD): $\delta = 1.22$ (d, $J = 7.2$ Hz, 6H), 1.78–1.98 (m, 4H), 3.24 (dd, $J = 8.7$, 13 Hz, 2H), 3.42–3.54 (m, 4H), 3.43 (dd, $J = 4.4$, 13 Hz, 2H), 3.96–4.11 (m, 2H), 6.93–7.00 (m, 2H), 7.18–7.26 (m, 4H), 7.30–7.36 ppm (m, 4H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 18.6$, 26.3, 47.0, 50.3, 51.5, 120.3, 123.7, 129.9, 140.7, 157.8, 158.3 ppm; HRMS (ESI): calcd for $C_{25}H_{36}N_7O_2$: 466.2931 $[M+H]^+$, found: 466.2910.

Compound 10l: $[\alpha]_D^{27} = -51.3$ ($c = 1.2$ in CH_3OH); ^1H NMR (400 MHz, CD_3OD): $\delta = 1.24$ (d, $J = 6.7$ Hz, 6H), 1.85–2.05 (m, 4H), 3.27 (dd, $J = 8.7$, 14 Hz, 2H), 3.41 (dd, $J = 4.6$, 14 Hz, 2H), 3.43–3.55 (m, 4H), 3.95–4.09 (m, 2H), 6.46–6.54 (m, 2H), 6.96–7.06 ppm (m, 4H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 18.6$, 26.4, 47.2, 50.3, 51.5, 97.9 (t, $J_{C-F} = 26$ Hz), 102.2 (d, $J_{C-F} = 30$ Hz), 143.7 (t, $J_{C-F} = 14$ Hz), 157.6, 157.8, 164.8 ppm (dd, $J_{C-F} = 15$, 244 Hz); HRMS (ESI): calcd for $C_{25}H_{32}F_4N_7O_2$: 538.2554 $[M+H]^+$; found: 538.2509.

Compound 10m: $[\alpha]_D^{27} = -10.8$ ($c = 1.2$ in CH_3OH); ^1H NMR (400 MHz, CD_3OD): $\delta = 1.24$ (d, $J = 7.2$ Hz, 6H), 1.86–2.02 (m, 4H), 3.28 (dd, $J = 8.2$, 13 Hz, 2H), 3.39 (dd, $J = 4.6$, 13 Hz, 2H), 3.44–3.52 (m, 4H), 3.93–4.14 (m, 2H), 7.24 (t, $J = 7.7$ Hz, 2H), 7.54 (t, $J = 8.2$ Hz, 2H), 7.62 (d, $J = 7.7$ Hz, 2H), 7.82 ppm (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 18.6$, 26.3, 47.2, 50.3, 51.6, 122.9 (q, $J_{C-F} = 29$ Hz), 125.3, 125.5 (q, $J_{C-F} = 272$ Hz), 127.1 (q, $J_{C-F} = 5.8$ Hz), 127.3, 133.8, 137.6, 157.7, 158.3 ppm; HRMS (ESI): calcd for $C_{27}H_{34}F_6N_7O_2$: 602.2678 $[M+H]^+$; found: 602.2728.

Compound 10n: $[\alpha]_D^{27} = -40.6$ ($c = 1.2$ in CH_3OH); ^1H NMR (400 MHz, CD_3OD): $\delta = 1.24$ (d, $J = 6.7$ Hz, 6H), 1.81–2.02 (m, 4H), 3.27 (dd, $J = 8.2$, 13 Hz, 2H), 3.40–3.55 (m, 4H), 3.43 (dd, $J = 4.4$, 13 Hz, 2H), 3.99–4.12 (m, 2H), 7.24 (br d, $J = 7.2$ Hz, 2H), 7.37–7.43 (m, 2H), 7.46 (br d, $J = 8.7$ Hz, 2H), 7.85 (s, 2H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 18.5$, 26.3, 47.1, 50.3, 51.6, 116.1 (q, $J_{C-F} = 3.9$ Hz), 119.7 (q, $J_{C-F} = 3.9$ Hz), 123.0, 125.7 (q, $J_{C-F} = 271$ Hz), 130.7, 132.0 (q, $J_{C-F} = 32$ Hz), 141.8, 157.9, 158.0 ppm; HRMS (ESI): calcd for $C_{27}H_{34}F_6N_7O_2$: 602.2678 $[M+H]^+$; found: 602.2723.

Compound 10o: $[\alpha]_D^{29} = -52.5$ ($c = 1.2$ in CH_3OH); ^1H NMR (400 MHz, CD_3OD): $\delta = 1.24$ (d, $J = 7.2$ Hz, 6H), 1.80–2.02 (m, 4H), 3.29 (dd, $J = 8.7$, 14 Hz, 2H), 3.43 (dd, $J = 4.4$, 14 Hz, 2H), 3.43–3.55 (m, 4H), 3.98–4.11 (m, 2H), 7.47–7.56 ppm (m, 8H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 18.6$, 26.3, 47.2, 50.4, 51.4, 119.3, 125.0 (q, $J_{C-F} = 32$ Hz), 125.9 (q, $J_{C-F} = 271$ Hz), 127.1 (q, $J_{C-F} = 3.9$ Hz), 144.5, 157.76, 157.84 ppm; HRMS (ESI): calcd for $C_{27}H_{34}F_6N_7O_2$: 602.2678 $[M+H]^+$; found: 602.2650.

Compound 10p: $[\alpha]_D^{27} = -40.8$ ($c = 1.3$ in CH_3OH); ^1H NMR (400 MHz, CD_3OD): $\delta = 1.22$ (d, $J = 6.7$ Hz, 6H), 1.80–2.00 (m, 4H), 3.24 (dd, $J = 8.7$, 13 Hz, 2H), 3.40–3.54 (m, 4H), 3.42 (dd, $J = 4.4$, 13 Hz, 2H), 3.94–4.09 (m, 2H), 6.92–7.01 (m, 4H), 7.29–7.35 ppm (m, 4H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 18.6$, 26.3, 47.1, 50.3, 51.5, 116.3 (d, $J_{C-F} = 22.3$ Hz), 122.1 (d, $J_{C-F} = 7.7$ Hz), 136.8 (d, $J_{C-F} = 2.3$ Hz), 157.8, 158.4, 160 ppm (d, $J_{C-F} = 240$ Hz); HRMS (ESI): calcd for $C_{25}H_{34}F_2N_7O_2$: 502.2742 $[M+H]^+$; found: 502.2724.

Compound 10q: $[\alpha]_D^{27} = -43.5$ ($c = 1.1$ in CH_3OH); ^1H NMR (400 MHz, CD_3OD): $\delta = 1.23$ (d, $J = 6.7$ Hz, 6H), 1.80–2.03 (m, 4H), 3.27 (dd, $J = 8.2$, 13 Hz, 2H), 3.42 (dd, $J = 4.6$, 13 Hz, 2H), 3.42–3.54 (m, 4H), 3.97–4.09 (m, 2H), 7.14 (br d, $J = 8.2$ Hz, 4H), 7.38–7.45 ppm (m, 4H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 18.6$, 26.3, 47.1, 50.3, 51.5, 121.1, 122.0 (q, $J_{C-F} = 255$ Hz), 122.8, 140.0, 145.3 (br), 157.8, 158.1 ppm; HRMS (ESI): calcd for $C_{27}H_{34}F_6N_7O_4$: 634.2577 $[M+H]^+$; found: 634.2576.

Compound 10r: $[\alpha]_D^{30} = -73.4$ ($c = 1.1$ in CH_3OH); ^1H NMR (400 MHz, CD_3OD): $\delta = 1.26$ (d, $J = 7.2$ Hz, 6H), 1.86–2.07 (m, 4H), 3.33 (dd, $J = 8.2$, 13 Hz, 2H), 3.42 (dd, $J = 4.6$, 13 Hz, 2H), 3.46–3.56 (m, 4H), 3.96–4.11 (m, 2H), 7.50–7.60 (m, 4H), 8.07–8.14 ppm (m, 4H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 18.5$, 26.4, 47.3, 50.4, 51.4, 118.6, 126.0, 143.3, 147.4, 157.3, 157.8 ppm; HRMS (ESI): calcd for $C_{25}H_{34}N_9O_6$: 556.2632 $[M+H]^+$; found: 556.2673.

Compound 10s: $[\alpha]_D^{27} = -56.9$ ($c = 1.1$ in CH_3OH); ^1H NMR (400 MHz, CD_3OD): $\delta = 1.22$ (d, $J = 6.7$ Hz, 6H), 1.78–2.01 (m, 4H), 3.22 (dd, $J = 8.5$, 13 Hz, 2H), 3.41–3.55 (m, 4H), 3.43 (dd, $J = 4.1$, 13 Hz, 2H), 3.73 (s, 6H), 3.95–4.07 (m, 2H), 6.75–6.86 (m, 4H), 7.13–7.22 ppm (m, 4H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 18.7$, 26.3, 47.1, 50.3, 51.4, 55.9, 115.2, 122.8, 133.4, 157.3, 157.8, 158.7 ppm; HRMS (ESI): calcd for $C_{27}H_{40}N_7O_4$: 526.3142 $[M+H]^+$; found 526.3174.

Synthesis of (+)-C20-desethylbenzyl camptothecin (13)

A solution of compound **5e** (822 mg, 2.0 mmol, 80% *ee*) in 80% aqueous TFA (25 mL) was stirred at room temperature for 1 h. The mixture was diluted with water and then extracted with $CHCl_3$. The organic extract was dried over $MgSO_4$, filtered, and then concentrated under reduced pressure to give ketone **4e**, which was used in the next step without purification. A mixture of crude ketone **4e**, 2-aminobenzaldehyde dimethylacetal (**12**) (6.0 mmol), *p*TsOH (0.02 mmol), and toluene (40 mL) was refluxed for 18 h by using a Dean–Stark trap under a nitrogen atmosphere, and then the reaction mixture was concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel ($CHCl_3$/ethyl acetate 2:1 to 1:1) to give a brown solid. The solid was recrystallized from methanol/acetonitrile to give (+)-C20-desethylbenzyl camptothecin (**13**) (130 mg, 16%, 2 steps). M.p. 247–250 °C (dec.); $[\alpha]_D^{26} = +54.8$ ($c = 0.5$ in DMF); ^1H NMR (400 MHz, [D$_6$]DMSO): $\delta = 3.19$ (dd, $J = 13.3$, 61.8 Hz, 2H), 3.51 (s, 1H), 4.77 (d, $J = 16.0$ Hz, 1H), 5.23–5.36 (m, 3H), 6.81 (s, 1H), 7.06–7.07 (m, 2H), 7.18–7.20 (m, 3H), 7.71 (t, $J = 7.8$ Hz, 1H), 7.86 (t, $J = 7.8$ Hz, 1H), 8.13 (t, $J = 7.8$ Hz, 2H), 8.68 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta = 44.3$, 50.1, 65.3, 72.9, 96.9, 119.6, 127.0, 127.6, 127.8, 128.4, 129.0, 129.6, 130.3, 130.4, 131.5, 134.0 ppm; HRMS (ESI): calcd for $C_{25}H_{18}N_2O_4Na$: 433.1164 $[M+Na]^+$; found: 434.1208; enantiomeric excess of **13** was determined to be >99% *ee* by chiral HPLC analysis: DAICEL Chiralpak IA column (250×4.6 mm), *n*-hexane/ethanol 60:40, flow rate: 0.2 mL min^{-1}, $\lambda = 220$ nm, $\tau_1 = 24.72$ (major), $\tau_2 = 23.61$ (minor).

Acknowledgements

This work was supported in part by a Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysts" (no. 23105013) from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and a Grant-in-Aid for Scientific Research (B) from JSPS (no. 20310130).

Keywords: camptothecin · guanidine · natural products · organocatalysis · urea

[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 – 3890.

[2] a) Y. H. Hsiang, R. Hertzberg, S. Hecht, L. F. Liu, *J. Biol. Chem.* **1985**, *260*, 14873 – 14878; b) Y. H. Hsiang, L. F. Liu, *Cancer Res.* **1988**, *48*, 1722 – 1726; c) B. L. Staker, K. Hjerrild, M. D. Feese, C. A. Behnke, A. B. Burgin Jr., L. Stewart, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 15387 – 15392; d) 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 – 4389.

[3] a) J. A. Gottlieb, A. M. Guarino, J. C. Call, V. T. Oliverio, J. B. Block, *Cancer Chemother. Rep.* **1970**, *54*, 461 – 470; b) C. G. Moertel, A. J. Schutt, R. J. Reitmeier, R. G. Hahn, *Cancer Chemother. Rep.* **1972**, *56*, 95 – 101; c) J. A. Gottlieb, J. K. Luce, *Cancer Chemother. Rep.* **1972**, *56*, 103 – 105.

[4] a) 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 – 107; b) D. Ormrod, C. M. Spencer, *Drugs* **1999**, *58*, 533 – 551; c) R. Riemsma, J. P. Simons, Z. Bashir, C. L. Gooch, J. Kleijnen, *BMC Cancer* **2010**, *10*, 436.

[5] 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 – 1168; b) Y. Kawato, M. Aonuma, Y. Hirata, H. Kuga, K. Sato, *Cancer Res.* **1991**, *51*, 4187 – 4191; c) S. Sawada, S. Okajima, R. Aiyama, K. Nokata, T. Furuta, T. Yokokura, E. Sugino, K. Yamaguchi, T. Miyasaka, *Chem. Pharm. Bull.* **1991**, *39*, 1446 – 1454; d) L. R. Wiseman, A. Markham, *Drugs* **1996**, *52*, 606 – 623.

[6] For a review on the synthesis of camptothecin and its analogues, see: W. Du, *Tetrahedron* **2003**, *59*, 8649 – 8687.

[7] For recent syntheses of camptothecin and its analogues, see: a) H. B. Zhou, G. S. Liu, Z. J. Yao, *Org. Lett.* **2007**, *9*, 2003 – 2005; b) L. P. Zhang, Y. Bao, Y. Y. Kuang, F. E. Chen, *Helv. Chim. Acta* **2008**, *91*, 2057 – 2061; c) G. S. Liu, Q. Li. Dong, Y. S. Yao, Z. J. Yao, *Org. Lett.* **2008**, *10*, 5393 – 5395; d) S. P. Chavan, A. N. Dhawane, U. R. Kalkote, *Tetrahedron Lett.* **2010**, *51*, 3099 – 3101; e) S. Yu, Q. Q. Huang, Y. Luo, W. Lu, *J. Org. Chem.* **2012**, *77*, 713 – 717; f) C. Wei, Z. Jiang, S. Tian, D. Zhang, *Tetrahedron Lett.* **2013**, *54*, 4515 – 4517; g) R. Peters, M. Althaus, C. Diolez, A. Rolland, E. Manginot, M. Veyrat, *J. Org. Chem.* **2006**, *71*, 7583 – 7595; h) R. Peters, C. Diolez, A. Rolland, E. Manginot, M. Veyrat, *Heterocycles* **2007**, *72*, 255 – 273.

[8] a) A. Ejima, H. Terasawa, M. Sugimori, H. Tagawa, *Tetrahedron Lett.* **1989**, *30*, 2639 – 2640; b) A. Ejima, H. Terasawa, M. Sugimori, H. Tagawa, *J. Chem. Soc. Perkin Trans. 1* **1990**, 27 – 31; c) T. Watanabe, Y. Tsuboi, S. Nomura, *Chem. Asian J.* **2013**, *8*, 630 – 638.

[9] a) D. L. Comins, M. F. Baevsky, H. Hong, *J. Am. Chem. Soc.* **1992**, *114*, 10971 – 10972; b) D. L. Comins, H. Hong, J. K. Saha, G. Jianhua, *J. Org. Chem.* **1994**, *59*, 5120 – 5121; c) D. L. Comins, H. Hong, G. Jianhua, *Tetrahedron Lett.* **1994**, *35*, 5331 – 5334; d) D. L. Comins, J. K. Saha, *Tetrahedron Lett.* **1995**, *36*, 7995 – 7998; e) D. L. Comins, J. M. Nolan, *Org. Lett.* **2001**, *3*, 4255 – 4257.

[10] a) F. G. Fang, S. Xie, M. W. Lowery, *J. Org. Chem.* **1994**, *59*, 6142 – 6143; b) D. P. Curran, S. B. Ko, H. Josien, *Angew. Chem.* **1995**, *107*, 2948 – 2950; *Angew. Chem. Int. Ed. Engl.* **1996**, *34*, 2683 – 2684; c) H. Josien, S. B. Ko, D. Bom, D. P. Curran, *Chem. Eur. J.* **1998**, *4*, 67 – 83; d) S. Jew, K. Ok, H. Kim, M. G. Kim, J. M. Kim, J. M. Hah, Y. Cho, *Tetrahedron: Asymmetry* **1995**, *6*, 1245 – 1248.

[11] a) K. Yabu, S. Masumoto, S. Yamasaki, Y. Hamashima, M. Kanai, W. Du, D. P. Curran, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 9908 – 9909; b) K. Yabu, S. Masumoto, M. Kanai, D. P. Curran, M. Shibasaki, *Tetrahedron Lett.* **2002**, *43*, 2923 – 2925; c) K. Yabu, S. Masumoto, M. Kanai, W. Du, D. P. Curran, M. Shibasaki, *Heterocycles* **2003**, *59*, 369 – 385.

[12] a) K. E. Henegar, S. W. Ashford, T. A. Baughman, J. C. Sih, R. L. Gu, *J. Org. Chem.* **1997**, *62*, 6588 – 6597; b) A. Imura, M. Itoh, A. Miyadera, *Tetrahedron: Asymmetry* **1998**, *9*, 2285 – 2291; c) A. Imura, M. Itoh, A. Miyadera, *Chem. Pharm. Bull.* **1998**, *46*, 1878 – 1880; d) M. C. Wani, A. W. Nicholas, M. E. Wall, *J. Med. Chem.* **1987**, *30*, 2317 – 2319.

[13] M. A. Ciufolini, F. Roschangar, *Angew. Chem.* **1996**, *108*, 1789 – 1791; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1692 – 1694.

[14] M. Odagi, K. Furukori, T. Watanabe, K. Nagasawa, *Chem. Eur. J.* **2013**, (chem.201303006), just accepted.

[15] a) Y. Sohtome, A. Tanatani, Y. Hashimoto, K. Nagasawa, *Adv. Synth. Catal.* **2005**, *347*, 1643 – 1648; b) Y. Sohtome, N. Takemura, T. Iguchi, Y. Hashimoto, K. Nagasawa, *Synlett* **2006**, 144 – 145; c) Y. Sohtome, Y. Hashimoto, K. Nagasawa, *Eur. J. Org. Chem.* **2006**, 2894 – 2867; d) Y. Sohtome, N. Takemura, T. Takada, R. Takagi, T. Iguchi, K. Nagasawa, *Chem. Asian J.* **2007**, *2*, 1150 – 1160; e) K. Takada, N. Nagasawa, *Adv. Synth. Catal.* **2009**, *351*, 345 – 347; f) S. Tanaka, K. Nagasawa, *Synlett* **2009**, 667 – 670; g) K. Takada, S. Tanaka, N. Nagasawa, *Synlett* **2009**, 1643 – 1646; h) Y. Sohtome, B. Shin, N. Horitsugi, R. Takagi, K. Noguchi, K. Nagasawa, *Angew. Chem.* **2010**, *122*, 7457 – 7461; *Angew. Chem. Int. Ed.* **2010**, *49*, 7299 – 7303; i) T. Sohtome, S. Tanaka, K. Takada, T. Yamaguchi, K. Nagasawa, *Angew. Chem.* **2010**, *122*, 9440 – 9443; *Angew. Chem. Int. Ed.* **2010**, *49*, 9254 – 9257;j) T. Sohtome, B. Shin, N. Horitsugi, K. Noguchi, K. Nagasawa, *Chem. Asian J.* **2011**, *6*, 2463 – 2470.

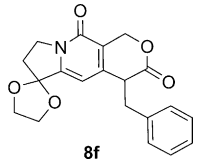
[16] For catalytic asymmetric α-hydroxylation of β-keto esters by using CHP as an oxidant, see: a) M. R. Acocella, O. G. MancheÇo, M. Bella, K. A. Jørgensen, *J. Org. Chem.* **2004**, *69*, 8165 – 8167; b) B. Gong, Q. Meng, T. Su, M. Lian, Q. Wang, Z. Gao, *Synlett* **2009**, 2659 – 2662; c) M. Lian, Z. Li, J. Du, Q. Meng, Z. Gao, *Eur. J. Org. Chem.* **2010**, 6525 – 6530; d) H. Yao, M. Lian, Z. Li, Y. Wang, Q. Meng, *J. Org. Chem.* **2012**, *77*, 9601 – 9608.

[17] For details of the synthesis of lactone **8b**–**8e**, see the Supporting Information.

[18] Catalysts used in the reaction were optimized for the substrates **8**.

[19] a) F. A. Davis, J. Lamendola Jr., U. Nadir, E. W. Kluger, T. C. Sedergran, T. W. Panunto, R. Billmers, R. Jenkins Jr., I. J. Turchi, *J. Am. Chem. Soc.* **1980**, *102*, 2000 – 2005; b) F. A. Davis, O. D. Stringer, *J. Org. Chem.* **1982**, *47*, 1774 – 1775; c) F. A. Davis, B. C. Chen, *Chem. Rev.* **1992**, *92*, 919 – 934.

[20] Oxidation did not proceed in the case of lactone **8f** because of its insolubility in toluene.



8f

[21] M. C. Wani, P. E. Ronman, J. T. Lindley, M. E. Wall, *J. Med. Chem.* **1980**, *23*, 554 – 560.

[22] Synthesis of (+)-C20-desethylbenzyl camptothecin (**13**), see the Supporting Information for details.

[23] For synthesis of (±)-C20-desethylbenzyl camptothecin (**13**), see: T. Sugasawa, T. Toyoda, N. Uchida, K. Yamaguchi, *J. Med. Chem.* **1976**, *19*, 675 – 679.

[24] Aniline **12** was prepared from 2-nitrobenzaldehyde dimethylacetal (R. Gopinath, S. J. Haque, B. K. Patel, *J. Org. Chem.* **2002**, *67*, 5842 – 5845) by catalytic hydrogenation in the presence of palladium charcoal in ethanol under ambient H_2 pressure.

[25] K. Nagasawa (Tokyo University of Agriculture and Technology), JP2009285556, **2009**.

[26] For details of the syntheses of compounds **15** and **16**, see the Supporting Information.

[27] A. Wittkopp, P. R. Schreiner, *Chem. Eur. J.* **2003**, *9*, 407 – 414.

Received: September 14, 2013
Published online on November 28, 2013