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Enantioselective Synthesis of 20(S)-Camptothecin Using Sharpless Catalytic Asymmetric Dihydroxylation

Sang-sup Jew,* Kwang-dae Ok, Hee-jin Kim, Myoung Goo Kim, Jong Min Kim, Jeong Mi Hah, and Youn-sang Cho

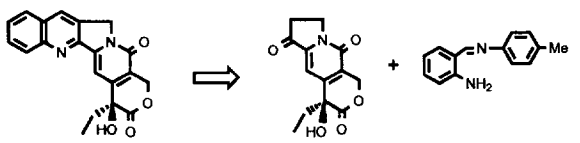
College of Pharmacy, Seoul National University, Kwanak-Ku,Seoul 151-742, Korea

Abstract: The homochiral key intermediate **2** of 20(S)-camptothecin was prepared enantioselectively by using catalytic asymmetric dihydroxylation as the key reaction.

20(S)-Camptothecin (**1**), a pentacyclic alkaloid isolated from *Camptotheca acuminata* by Wall and co-workers in 1966,[1] has potent antitumor activity against various cell lines and in animal screens.[2] Only the (S)-enantiomer **1** exhibits antitumor activity [3] and its mode of action was found to trap a cleavable complex between topoisomerase I and DNA.[4]

A number of successful syntheses of **1** have so far been reported, [1,5] but most of the syntheses are racemic. To date five enantioselective syntheses of **1** have been reported; two employ resolution,[3,6e] two use a chiral auxiliary,[6b,c,d] and one uses a chiral catalyst.[6a] The synthesis reported by Tagawa connects the chiral synthetic key intermediate, hydroxy lactone **2**, and amine **3** to afford **1** [5e,6d] (Scheme 1). We have taken much interest in the Tagawa's efficient route and its potential for application to the enantioselective synthesis of

Scheme 1

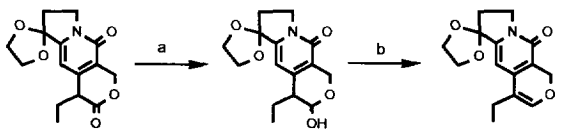


1 **2** **3**

therapeutically useful analogs of camptothecin. However, stoichiometric use of the expensive chiral auxiliary, N-tosyl-(R)-proline that is required, limits practical access to large quantities of the key intermediate **2**.

In this paper, we report a novel and practical asymmetric synthesis of **2** by using the catalytic asymmetric dihydroxylation(AD)[7] recently developed by Sharpless et.al. The substrate for the AD reaction, the endocyclic enol ether **6**, was prepared from lactone **4** [8] as shown in Scheme 2. The carbonyl group of **4** [8] was reduced with DIBAL-H in THF to give the lactol **5**, which was dehydrated via its mesylate to afford **6**.

Scheme 2

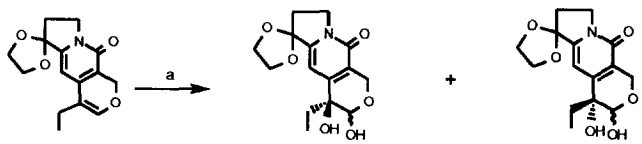


4 **5** **6**

Reagents and conditions : (a) DIBAL-H (1.2eq), THF, -78°C, 2h (94%) ; (b) MsCl (4.0eq), TEA (8.0eq), THF, rt, 24h, (96%).

The asymmetric dihydroxylations of **6** with catalytic chiral ligands, $(DHQD)_2$ -PHAL,[9a] $(DHQD)_2$ -PYR, [9b] DHQD-PHN,[9c] DHQD-MEQ, [9c] DHQD-CLB,[9c] $(DHQ)_2$-PHAL,[9a] and $(DHQ)_2$-PYR[9b] were performed according to the standard procedure to give inseparable mixtures of hydroxy lactols **7** and **8** in 29-89% yields (Scheme 3, Table 1). The products from dihydroxylation should be a pair of enantiomers, however, both **7** and **8** were obtained as diastereomeric mixtures, due to the anomeric carbon. The ratio of **7** to **8** was calculated based on the integration of the anomeric proton in the ^{1}H-NMR spectra of the derived MTPA esters.[10] The absolute configurations of **7** and **8** were assigned by comparison of the specific rotation of **2** obtained as shown in Scheme 4, with the literature values (*vide infra*).[11]

Scheme 3



6 **7** **8**

Reagents and conditions:(a) Chiral ligand (0.01eq), $K_3Fe(CN)_6$ (3.0eq), K_2CO_3 (3.0eq), $K_2OsO_2(OH)_4$ (0.002eq), $CH_3SO_2NH_2$ (1.0eq), t-BuOH:H_2O = 1:1, 0° C

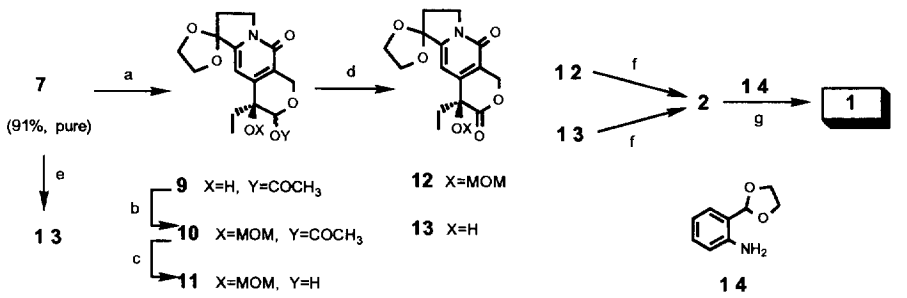
Table 1.

Entry	Ligand	Reaction time (hr)	7 : 8	Yield (%)
1	$(DHQD)_2$-PHAL	96	91 : 9	89
2	$(DHQD)_2$-PYR	18	92 : 8	74
3	DHQD-PHN	24	85 : 15	54
4	DHQD-MEQ	24	85 : 15	51
5	DHQD-CLB	24	74 : 26	29
6	$(DHQ)_2$-PHAL	120	11 : 89	66
7	$(DHQ)_2$-PYR	18	3 : 97	71

As expected from the Sharpless model[7], DHQD ligands gave **7** as major products (the ratio of **7** to **8**, 74:26 ~ 92:8) (Entry 1-5) while DHQ ligands afforded **8** preferentially (the ratio of **7** to **8**, 11:89 ~ 3:97). Of the chiral ligands, PHAL[9a] and PYR[9b] ligands gave better results than other ligands (Entry 1, 2, 6, 7). Especially, in the case of **7** which is required for the synthesis of **1**, $(DHQD)_2$-PHAL and $(DHQD)_2$-PYR surpass other chiral ligands with respect to the enantiofacial selectivity and chemical yield.

Compound **7** (91% pure, Entry 1) was oxidized directly with iodine in the presence of calcium carbonate [12] to give α-hydroxy lactone **13** (mp 167.5~169°C, $[\alpha]_D^{20}$ +88.0, c 0.443, $CHCl_3$), however, in an unsatisfactory yield (48%). To improve the yield of the oxidation, we planned to oxidize the secondary hydroxyl group after protection of the tertiary hydroxy group of **7** in consideration of possible cleavage of 1,2-diol under usual oxidative conditions. Thus, selective acylation of **7** with acetic anhydride in pyridine at room temperature gave acetate **9**, which was treated with chloromethyl methyl ether and N,N-diisopropylethylamine to afford **10**. Compound **10** was hydrolyzed to give deacylated product **11**. Subsequent oxidation of **11** with pyridinium chlorochromate and sodium acetate in the presense of 4A molecular sieves gave oxidized product **12** ($[\alpha]_D^{26}$ -12.8, c 0.695, $CHCl_3$). This was treated with HCl in THF-H_2O to simultaneously cleave the ketal and the methoxymethyl groups to provide **2** (mp 165~166°C, $[\alpha]_D^{20}$ +98.8, c 0.477, $CHCl_3$), (lit.[11] $[\alpha]_D^{20}$ +120.6, $CHCl_3$) (61% yield, from **7**). The α-hydroxy lactone **13** was also converted to **2** by hydrolysis with HCl (Scheme 4).

Scheme 4



Reagents and conditions : (a) $(CH_3CO)_2O$ (20.0eq), Pyr, rt, 3h (85%) ; (b) CH_3OCH_2Cl (15.0eq), i-Pr_2NEt (20.0eq), CH_2Cl_2, rt, 3days, (93%) ; (c) K_2CO_3 (2.0eq), MeOH:H_2O = 5:1, rt, 2h (92%) ; (d) pyridinium chlorochromate (4.0eq), $NaOCOCH_3$ (10.0eq), Molecular sieves 4A, rt, 24h (84%) ; (e) I_2 (10.0eq), $CaCO_3$ (10.0eq), MeOH:H_2O = 10:1, rt, 24h (48%); (f) c-HCl (120.0eq), THF:H_2O = 2:1, 60°C, 3h (100%) ; (g) **14** (1.0eq), PTSA (cat.), toluene, reflux, 3h (69%).

From the specific rotation, we can conclude that the absolute configuration of **2** concerning the carbon bearing the tertiary hydroxy group should be (S) and the enantiomeric excess corresponds to 82% (*vide supra*). The Friedlander condensation of **2** and amine **14**[14] was performed in the presence of PTSA by refluxing in toluene to provide **1** (mp 263~266°C, $[\alpha]_D^{20}$ +33.8, c 0.125, $CHCl_3$:MeOH = 4:1) (lit. $[\alpha]_D^{20}$ +40.7[13a], +42.0[5c], +42.8[13b,c]; $CHCl_3$:MeOH = 4:1). Our synthetic **1** was identical with authentic material[5c] in all respects.

Futher studies are in progress to improve the overall yield of this synthetic scheme and to develop more efficient route to the substrate **6** for the AD.

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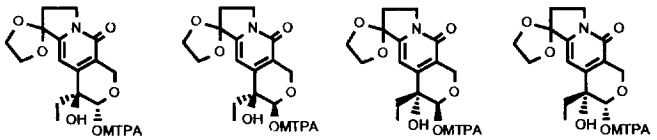
10. a) Treatment of the mixture of **7** and **8** (Entry 1) with (S)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetyi chloride (MTPA-Cl) and DMAP in THF at rt for 2h[11b] gave a mixture of the MTPA esters, trans-MTPA esters (**7a**+**8a**) and cis-MTPA esters (**7b**+**8b**) in 6.9:1 (or 1:6.9) (85%) after silica gel chromatography (Rf=0.38 and 0.33; methanol:methylene chloride = 1:20). From the ^{1}H-NMR (400 MHz) spectra of trans esters (**7a**+**8a**) and cis esters (**7b**+**8b**),the ratio of **7a** to **8a** and that of **7b** to **8b** were estimated both as 91:9 by comparing the integration of 4 anomeric protons [δ **7a** (6.40), **8a** (6.33), **7b** (6.32), **8b** (6.34)].In other cases too, the same procedures were performed and the results are summarized in Table 1.



7a **7b** **8a** **8b**

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