HETEROCYCLES, Vol. 53, No. 4, 2000, pp. 771 - 775, Received, 14th January, 2000

ASYMMETRIC SYNTHESES OF (+)-CAMPTOTHECIN AND (+)-7-ETHYL-10-METHOXYCAMPTOTHECIN

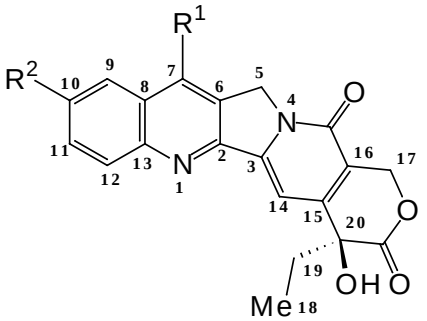
Keiko Tagami,[a] Norio Nakazawa,[b] Shigeki Sano,[b] and Yoshimitsu Nagao*[b]

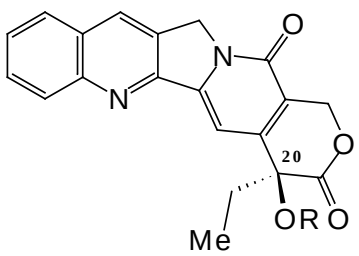
[a] Faculty of Pharmaceutical Sciences, Mukogawa Women's University, 11-68 Koshien Kyuban-cho, Nishinomiya, Hyogo 663-8179, Japan

[b] Faculty of Pharmaceutical Sciences, The University of Tokushima, Sho-machi, Tokushima 770-8505, Japan

Abstract- Total syntheses of (+)-camptothecin (**1a**) and (+)-7-ethyl-10-methoxy-camptothecin (**1b**) from racemic ethyl 1-ethoxycarbonyl-3-oxopyrrolidin-2-ylacetate (**7**) were accomplished *via* asymmetric hydroxylation onto C20 of racemic 20-deoxycamptothecin derivatives (**3a**,**b**) employing a chiral Davis reagent, (2*R*, 8a*S*)-(+)-(camphorylsulfonyl)oxaziridine.

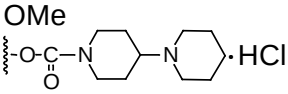
Since discovery of (+)-camptothecin (**1a**) as a potent antitumor-active alkaloid from *Campthotheca acuminata* by Wall and co-workers in 1966,[1] its synthesis and chemical modification have extensively been performed in the world.[2] Irinotecan (**1c**)[2l,3] and (2'*S*, 3'*R*)- and (2'*R*, 3'*S*)-dihydroxybutanoylcamptothecin derivatives (**2a,b**)[4] have proved to be more superior tumor inhibitors as compared to (+)-camptothecin (**1a**) itself. Thus, we have investigated and estasblished a new synthetic procedure for (+)-camptothecin (**1a**) and (+)-7-ethyl-10-methoxycamptothecin (**1b**), a key intermediate toward the synthesis of irinotecan like compounds.

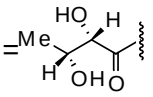
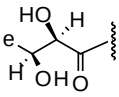




1a $R^1 = R^2 = H$ **(+)-camptothecin**

1b R^1 = Et, R^2 = OMe

1c R^1 = Et, R^2 =  · HCl $3H_2O$ **irinotecan**

2a R =  **2b** R = 

As shown in Figure 1, enolization of 20-deoxycamptothecin derivatives (**3a**,**b**) followed by asymmetric hydroxylation at the C20 position is featured in our synthetic access to the goal because this strategy will be applicable to the development of various C20-functionalized camptothecin analogs (**4a**,**b**) by exploiting suitable electrophiles [$E^+ = RS^+$, X^+ (X = Br, I), etc.]. The 20-deoxycamptothecin derivatives (**3a**,**b**) can be synthesized by intermolecular dehydrative condensation between compounds (**5a**,**b**) and **6**, respectively.[2h]

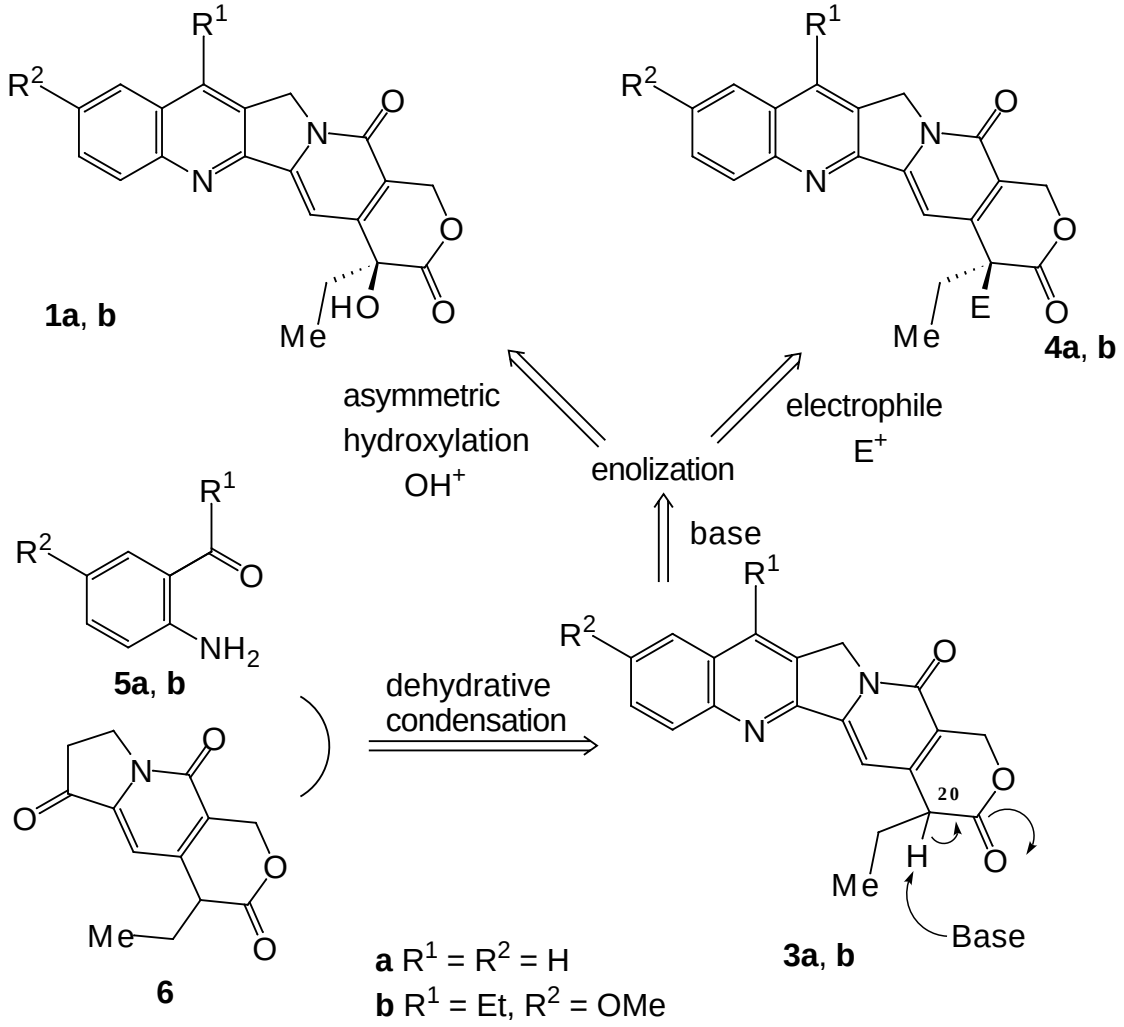
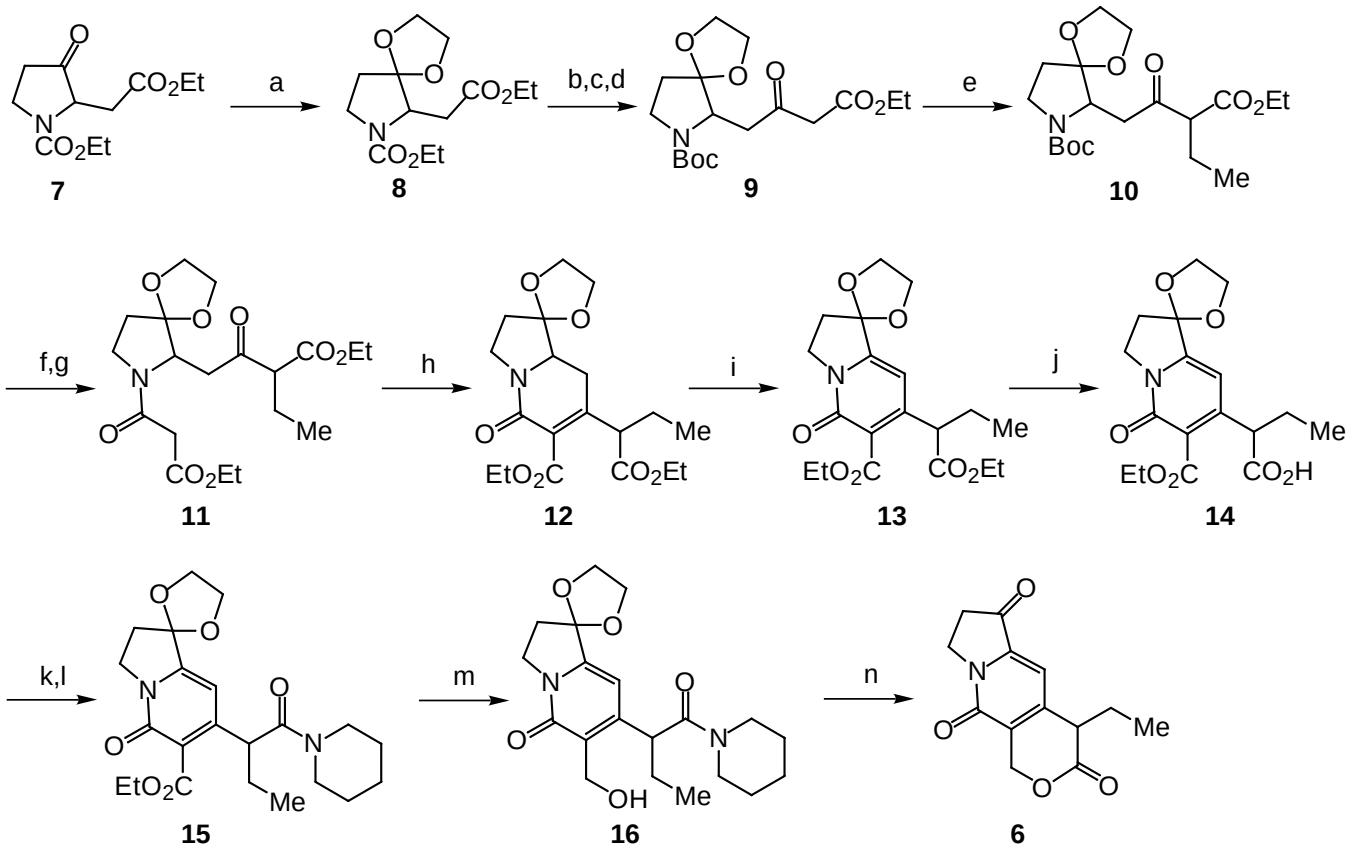


Figure 1. Synthetic strategy of camptothecin derivatives (**1a**,**b** and **4a,b**)

The key compound (**6**)[2h] was successfully synthesized starting from known pyrrolidinone (**7**)[5] as shown in Scheme 1. Ketalization of **7** with ethylene glycol under the conventional conditions gave dioxolane (**8**) in 84% yield. Alkaline hydrolysis of **8** with 20% KOH - EtOH (1:1) under reflux followed by protection of pyrrolidine amino group with Boc_2O and 1M NaOH in dioxane and then treatment of the resulting *N*-Boc carboxylic acid with the Masamune reagent system[6] afforded keto ester (**9**) in 71% overall yield from **8**. After ethylation of **9** with EtI - NaH in DMF, the resulting compound (**10**) (75% yield) was subjected to the usual deprotection of the *N*-Boc group and then treated with ethyl malonyl chloride in the presence of Et_3N-DMAP in benzene to give *N*-malonyl amide (**11**) in 88% yield. Selective Dieckmann-type condensation of **11** with a catalytic amount of EtONa smoothly proceeded in refluxing EtOH to furnish the

desired cyclized product (**12**) in 71% yield as a diastereomeric mixture. Oxidative dehydrogenation of **12** with DDQ in dioxane under reflux afforded pyridone (**13**) (87% yield), which was subjected to alkaline hydrolysis with 10% NaOH in EtOH at 0˚C to give selectively monocarboxylic acid (**14**) as a colorless solid [mp 148-150˚C (AcOEt)] in 81% yield. Treatment of **14** with ethyl chloroformate in the presence of Et_3N in THF at 0˚C followed by aminolysis of the resulting mixed anhydride with piperidine gave amide (**15**) in 70% yield. Reduction of **15** with $LiBH_4$ in dioxane turned out to be alcohol (**16**) (55% yield), which was treated with 6N HCl under reflux to provide the desired δ-lactone (**6**) [mp 160-161˚C (AcOEt); lit.,[2h] mp 162-163˚C (AcOEt)] as colorless needles in 60% yield.

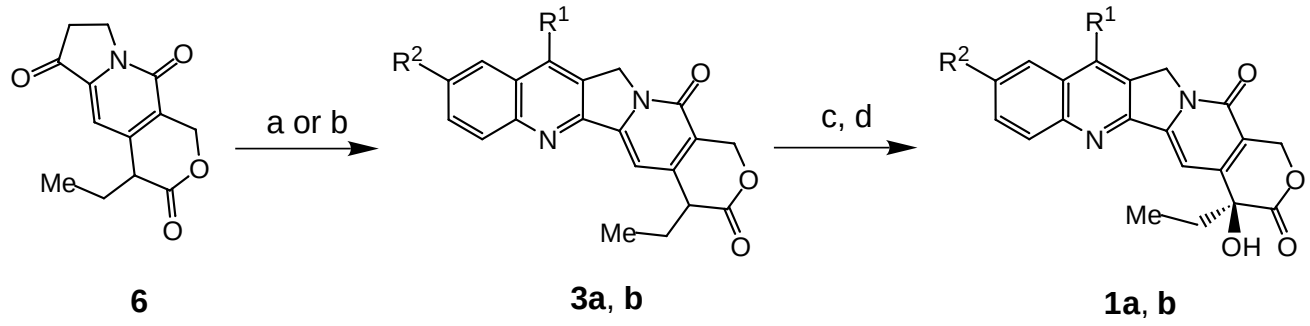
Scheme 1



Reagents and conditions : a) ethylene glycol (1.1 mol eq), TsOH (cat.), benzene, reflux, 4 h; b) 20% aq. KOH / EtOH (1:1), reflux, 12 h; c) Boc_2O (1.5 mol eq), 1M NaOH (1.5 mol eq), dioxane, rt, 12 h; d) $CO(Im)_2$ (1.2 mol eq), $EtO_2CCH_2CO_2K$ (2.2 mol eq), $MgCl_2$ (1.2 mol eq), Et_3N (2.4 mol eq), THF, rt, 24 h; e) NaH (1.2 mol eq), EtI (1.2 mol eq), DMF, rt, 3 h; f) TFA / anisole (2:1), 0 ˚C, 30 min; g) $ClCOCH_2CO_2Et$ (1.2 mol eq), Et_3N (2.5 mol eq), DMAP (0.4 mol eq), benzene, rt, 1 h; h) EtONa (0.05 mol eq), EtOH, reflux, 1 h; i) DDQ (1.0 mol eq), dioxane, reflux, 4 h; j) 10% NaOH (3.0 mol eq), EtOH, 0 ˚C, 6 h; k) $ClCO_2Et$ (1.5 mol eq), Et_3N (3.0 mol eq), THF, 0 ˚C, 30 min; l) piperidine (1.5 mol eq), THF, rt, 1 h; m) $LiBH_4$ (4.0 mol eq), dioxane, rt, 30 min; n) 6N HCl, reflux, 30 min

Dehydrative condensation of **6** with 2-aminobenzaldehyde (**5a**) in the presence of morpholine in refluxing toluene afforded racemic 20-deoxycamptothecin (**3a**) [mp 256-260˚C ($CHCl_3$-AcOEt); lit.,[2b] mp 258-264˚C] as a yellow solid in 64% yield as shown in Scheme 2. Similar condensation of **6** with 2'-amino-5'-methoxypropiophenone (**5b**) [yellow needles, mp 58˚C (CH_2Cl_2-hexane)] obtained from the reaction of *p*-anisidine with propionitrile utilizing the Sugasawa method,[7] was done in the presence of a catalytic amount of TsOH in toluene under reflux to give racemic 7-ethyl-10-methoxy-20-deoxycamptothecin (**3b**) [mp 276-278˚C ($CHCl_3$-AcOEt)] as yellow needles in 60% yield. Davis and Weismiller reported that the enolate generated by treatment of 3-isochromanone with NHMDS, was allowed to react with (2*R*,8a*S*)-(+)-(camphorylsulfonyl)oxaziridine to give the *S*-hydroxy derivative in 77% ee.[8] The δ-lactone moiety of **3a**,**b** seemed to be similar to that of 3-isochromanone. Thus, asymmetric hydroxylation at C20 of **3a**,**b** was attempted by exploiting a chiral Davis reagent, *N*-sulfonyloxaziridine as follows. After enolization of **3a**,**b** with LHMDS in THF at -78˚C, each resulting enolate was treated with (2*R*,8a*S*)-(+)-(camphorylsulfonyl)oxaziridine[8] to furnish the corresponding (+)-camptothecin (**1a**) {mp 264-266˚C decomp (MeCN-MeOH), $[\alpha]_D^{25}$ +14.2˚ [*c* 0.34, $CHCl_3$-MeOH (4 : 1)]; lit.,[1] mp 264-267˚C decomp (MeCN-MeOH), $[\alpha]_D^{25}$ +31.3˚ [$CHCl_3$-MeOH (4 : 1)]} as a pale yellow solid in 53% yield and (+)-7-ethyl-10-methoxycamptothecin (**1b**) {mp 276-278˚C ($CHCl_3$-AcOEt), $[\alpha]_D^{25}$ +27.4˚ [*c* 0.46, $CHCl_3$-MeOH (4 : 1)]; the authentic compound[9] mp 279-281˚C ($CHCl_3$-AcOEt), $[\alpha]_D^{25}$ +38.7˚ [*c* 0.51, $CHCl_3$-MeOH (4 : 1)]} as pale yellow needles in 40% yield, respectively, as shown in Scheme 2. Spectroscopic data (^{1}H NMR, IR, and MS) of synthetic compounds (**1a**,**b**) were identical with those of the authentic (+)-camptothecin and (+)-7-ethyl-10-methoxycamptothecin.[9]

Scheme 2



6 **3a**, **b** **1a**, **b**

Reagents and conditions: a) 2-aminobenzaldehyde (**5a**) (1.5 mol eq), morpholine (1.5 mol eq), toluene, reflux, 3 h; b) 2'-amino-5'-methoxypropiophenone (**5b**) (1 mol eq), TsOH (0.1 mol eq), toluene, reflux, 3 h; c) $[(CH_3)_3Si]_2NLi$ (1.5 mol eq), THF, -78 ˚C, 30 min; d) (2*R*, 8a*S*)-(+)-(camphorylsulfonyl)oxaziridine (1.5 mol eq), THF, -78 ˚C, 3 h

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9. We greatly appreciate Dr. S. Sawada, Yakult Institute for Microbiological Research for the gifts of the authentic (+)-camptothecin and (+)-7-ethyl-10-methoxycamptothecin.