

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

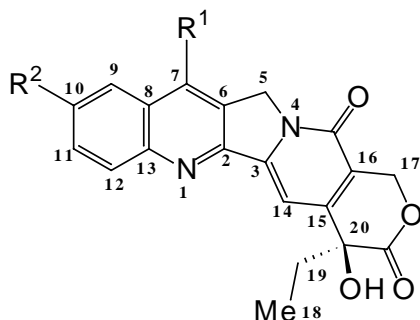
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
**Abstract-** Total syntheses of (+)-camptothecin (**1a**) and (+)-7-ethyl-10-methoxy-  
camptothecin (**1b**) from racemic ethyl 1-ethoxycarbonyl-3-oxopyrrolidin-2-  
ylacetate (**7**) were accomplished *via* asymmetric hydroxylation onto C20 of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

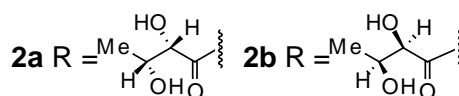
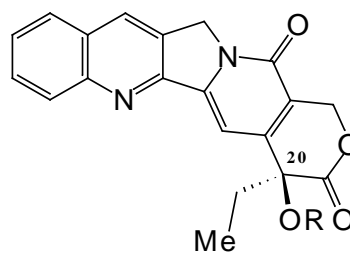
Since discovery of (+)-camptothecin (**1a**) as a potent antitumor-active alkaloid from *Camptotheca acuminata* by Wall and co-workers in 1966,<sup>1</sup> its synthesis and chemical modification have extensively been performed in the world.<sup>2</sup> Irinotecan (**1c**)<sup>21,3</sup> and (2'*S*, 3'*R*)- and (2'*R*, 3'*S*)-dihydroxybutanoylcamptothecin derivatives (**2a,b**)<sup>4</sup> have proved to be more superior tumor inhibitors as compared to (+)-camptothecin (**1a**) itself. Thus, we have investigated and established 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<sup>1</sup> = R<sup>2</sup> = H (+)-camptothecin

**1b** R<sup>1</sup> = Et, R<sup>2</sup> = OMe

**1c** R<sup>1</sup> = Et, R<sup>2</sup> =  · HCl · 3H<sub>2</sub>O irinotecan



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.<sup>2h</sup>

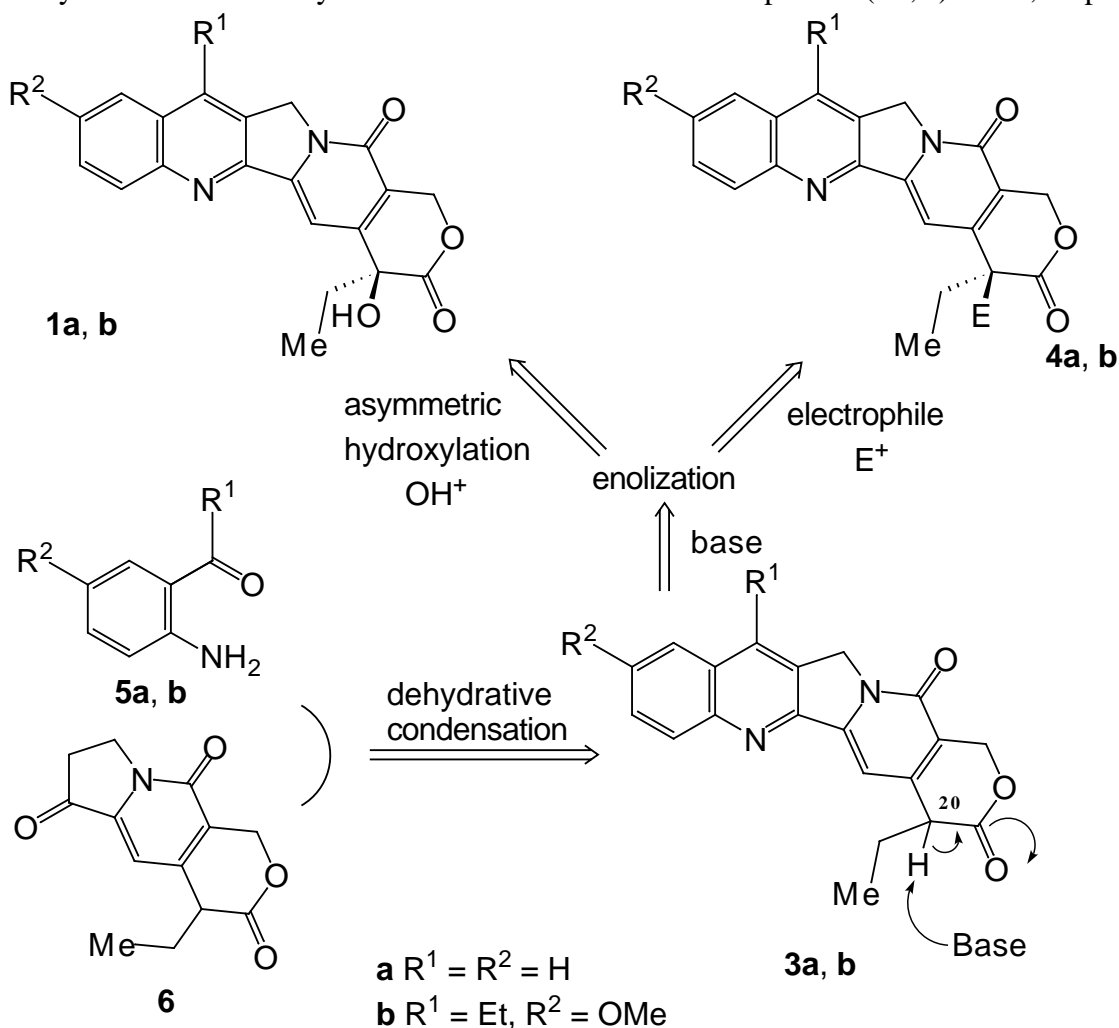
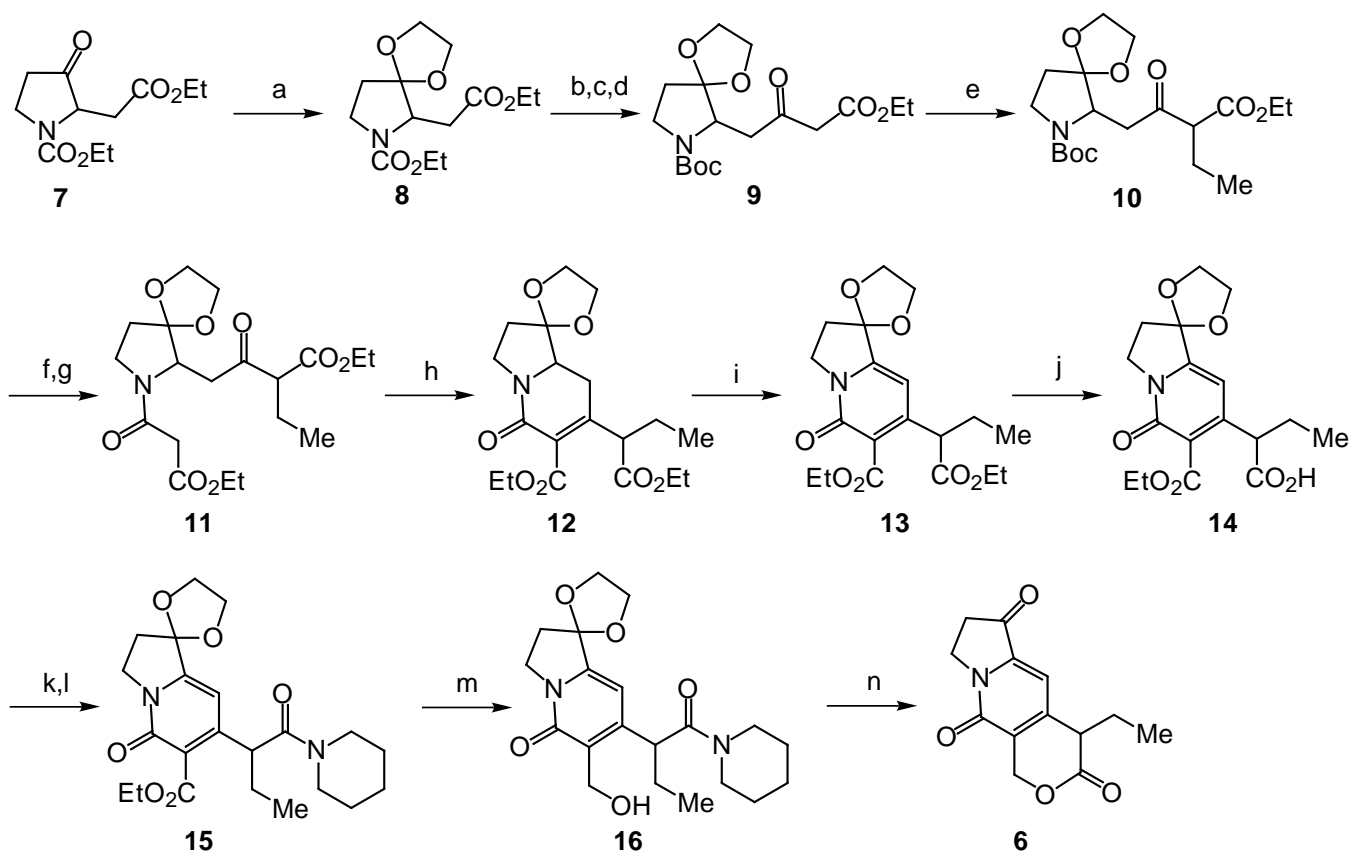


Figure 1. Synthetic strategy of camptothecin derivatives (**1a,b** and **4a,b**)

The key compound (**6**)<sup>2h</sup> was successfully synthesized starting from known pyrrolidinone (**7**)<sup>5</sup> 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<sup>6</sup> 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<sub>3</sub>N 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<sub>4</sub> in dioxane turned out to be alcohol (**16**) (55% yield), which was treated with 6N HCl under reflux to provide the desired  $\delta$ -lactone (**6**) [mp 160-161°C (AcOEt); lit.,<sup>2h</sup> mp 162-163°C (AcOEt)] as colorless needles in 60% yield.

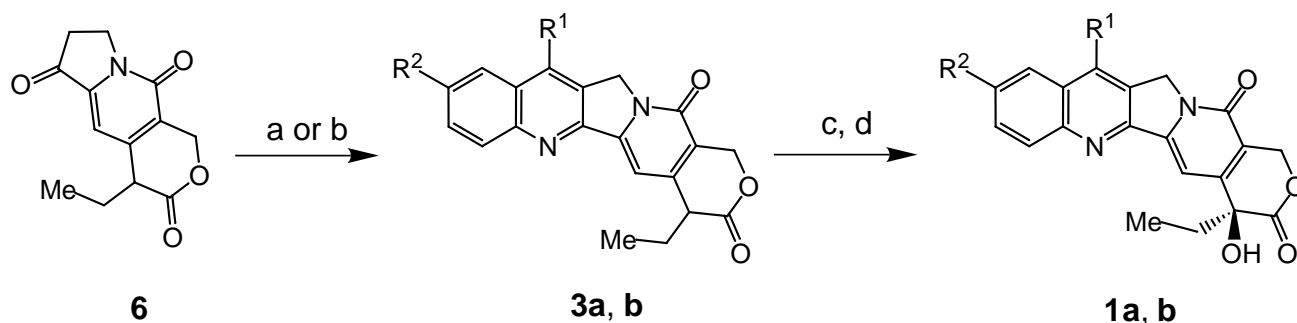
**Scheme 1**



**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<sub>2</sub>O (1.5 mol eq), 1M NaOH (1.5 mol eq), dioxane, rt, 12 h; d) CO(lm)<sub>2</sub> (1.2 mol eq), EtO<sub>2</sub>CCH<sub>2</sub>CO<sub>2</sub>K (2.2 mol eq), MgCl<sub>2</sub> (1.2 mol eq), Et<sub>3</sub>N (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<sub>2</sub>CO<sub>2</sub>Et (1.2 mol eq), Et<sub>3</sub>N (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<sub>2</sub>Et (1.5 mol eq), Et<sub>3</sub>N (3.0 mol eq), THF, 0 °C, 30 min; l) piperidine (1.5 mol eq), THF, rt, 1 h; m) LiBH<sub>4</sub> (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<sub>3</sub>-AcOEt); lit.,<sup>2b</sup> 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<sub>2</sub>Cl<sub>2</sub>-hexane)] obtained from the reaction of *p*-anisidine with propionitrile utilizing the Sugasawa method,<sup>7</sup> 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<sub>3</sub>-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*,8*aS*)-(+)-(camphorylsulfonyl)oxaziridine to give the *S*-hydroxy derivative in 77% ee.<sup>8</sup> The  $\delta$ -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*,8*aS*)-(+)-(camphorylsulfonyl)oxaziridine<sup>8</sup> to furnish the corresponding (+)-camptothecin (**1a**) {mp 264-266°C decomp (MeCN-MeOH), [ $\alpha$ ]<sub>D</sub><sup>25</sup> +14.2° [*c* 0.34, CHCl<sub>3</sub>-MeOH (4 : 1)]; lit.,<sup>1</sup> mp 264-267°C decomp (MeCN-MeOH), [ $\alpha$ ]<sub>D</sub><sup>25</sup> +31.3° [CHCl<sub>3</sub>-MeOH (4 : 1)]} as a pale yellow solid in 53% yield and (+)-7-ethyl-10-methoxycamptothecin (**1b**) {mp 276-278°C (CHCl<sub>3</sub>-AcOEt), [ $\alpha$ ]<sub>D</sub><sup>25</sup> +27.4° [*c* 0.46, CHCl<sub>3</sub>-MeOH (4 : 1)]; the authentic compound<sup>9</sup> mp 279-281°C (CHCl<sub>3</sub>-AcOEt), [ $\alpha$ ]<sub>D</sub><sup>25</sup> +38.7° [*c* 0.51, CHCl<sub>3</sub>-MeOH (4 : 1)]} as pale yellow needles in 40% yield, respectively, as shown in Scheme 2. Spectroscopic data (<sup>1</sup>H NMR, IR, and MS) of synthetic compounds (**1a,b**) were identical with those of the authentic (+)-camptothecin and (+)-7-ethyl-10-methoxycamptothecin.<sup>9</sup>

**Scheme 2**



*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<sub>3</sub>)<sub>3</sub>Si]<sub>2</sub>NLi (1.5 mol eq), THF, -78 °C, 30 min; d) (2*R*,8*aS*)-(+)-(camphorylsulfonyl)oxaziridine (1.5 mol eq), THF, -78 °C, 3 h

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