ASYMMETRIC SYNTHESES 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, (2R, 8aS)-(+)-(camphorylsulfonyl)oxaziridine.

Since discovery of (+)-camptothecin (1a) as a potent antitumor-active alkaloid from Campthotheca acuminata by Wall and co-workers in 1966, its synthesis and chemical modification have extensively been performed in the world. Irinotecan (1c) and (2'S, 3'R)- and (2'R, 3'S)-dihydroxybutanoylcamptothecin derivatives (2a,b) 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.
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 \([E^+ = RS^+, X^+ (X = Br, I), \text{etc.}]\). The 20-deoxycamptothecin derivatives (3a, b) can be synthesized by intermolecular dehydrative condensation between compounds (5a, b) and 6, respectively.\(^2\)

![Figure 1. Synthetic strategy of camptothecin derivatives (1a,b and 4a,b)](image)

The key compound (6)\(^2\) 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 Boc₂O 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 Et₃N-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$_3$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$_4$ 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$_2$O (1.5 mol eq), 1M NaOH (1.5 mol eq), dioxane, rt, 12 h; d) CO(Im)$_2$ (1.2 mol eq), EtO$_2$CCH$_2$CO$_2$K (2.2 mol eq), MgCl$_2$ (1.2 mol eq), Et$_3$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) CI COCH$_2$CO$_2$Et (1.2 mol eq), Et$_3$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) CI CO$_2$Et (1.5 mol eq), Et$_3$N (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 (CHCl₃-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'-methoxypropophenone (5b) [yellow needles, mp 58°C (CH₂Cl₂-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 (CHCl₃-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 (2R,8aS)-(+)-(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 (2R,8aS)-(+)-(camphorylsulfonyl)oxaziridine ⁸ to furnish the corresponding (+)-camptothecin (1a) [mp 264-266°C decmp (MeCN-MeOH), [α]₁₀⁺₂⁵ +14.2° [c 0.34, CHCl₃-MeOH (4 : 1)]; lit., ¹ mp 264-267°C decmp (MeCN-MeOH), [α]₁₀⁺₂⁵ +31.3° [CHCl₃-MeOH (4 : 1)]] as a pale yellow solid in 53% yield and (+)-7-ethyl-10-methoxyacamptothecin (1b) [mp 276-278°C (CHCl₃-AcOEt), [α]₁₀⁺₂⁵ +27.4° [c 0.46, CHCl₃-MeOH (4 : 1)]; the authentic compound ⁹ mp 279-281°C (CHCl₃-AcOEt), [α]₁₀⁺₂⁵ +38.7° [c 0.51, CHCl₃-MeOH (4 : 1)]] as pale yellow needles in 40% yield, respectively, as shown in Scheme 2. Spectroscopic data (¹H NMR, IR, and MS) of synthetic compounds (1a,b) were identical with those of the authentic (+)-camptothecin and (+)-7-ethyl-10-methoxyacamptothecin. ⁹

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'-methoxypropophenone (5b) (1 mol eq), TsOH (0.1 mol eq), toluene, reflux, 3 h; c) [(CH₃)₃Si]₂NLi (1.5 mol eq), THF, -78 °C, 30 min; d) (2R, 8aS)-(+)-(camphorylsulfonyl)oxaziridine (1.5 mol eq), THF, -78 °C, 3 h
REFERENCES AND NOTES


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