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A Practical and Efficient Synthesis of (±)- Camptothecin#

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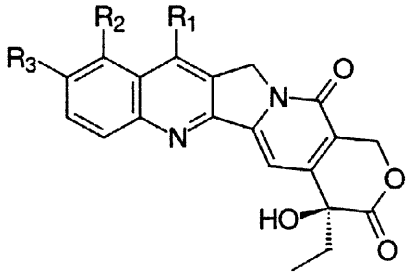
Abstract:

A practical and efficient synthesis of (±)-camptothecin from glycine *via* an intramolecular Michael addition is described.

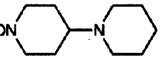
Keywords: glycine; Wittig reaction; intramolecular Michael reaction; DIBAL-H reduction; camptothecin

The search for practical yet efficient syntheses of bioactive molecules has been the focus of our interest. In this connection, camptothecin **1**[1] was chosen as a target molecule owing to its anticancer properties.

Camptothecin **1** has regained its position as a leading candidate in cancer chemotherapy with the development of certain derivatives *viz.* Topotecan[2] and Irinotecan[2] which have proved to be far superior as compared to the parent compound **1**. Although a number of syntheses[3-9] of camptothecin have appeared following its initial isolation by Wall *et al.*, none is practical enough for large scale synthesis. Thus, there is a need for a more practical and efficient synthesis of camptothecin.



1 R_1=R_2=R_3=H **Camptothecin**

2 R_1=Et, R_2=H, R_3=  ·HCl $3H_2O$ **Irinotecan**

3 R_1=H, R_2=CH_2NMe_2.HCl, R_3=OH **Topotecan**

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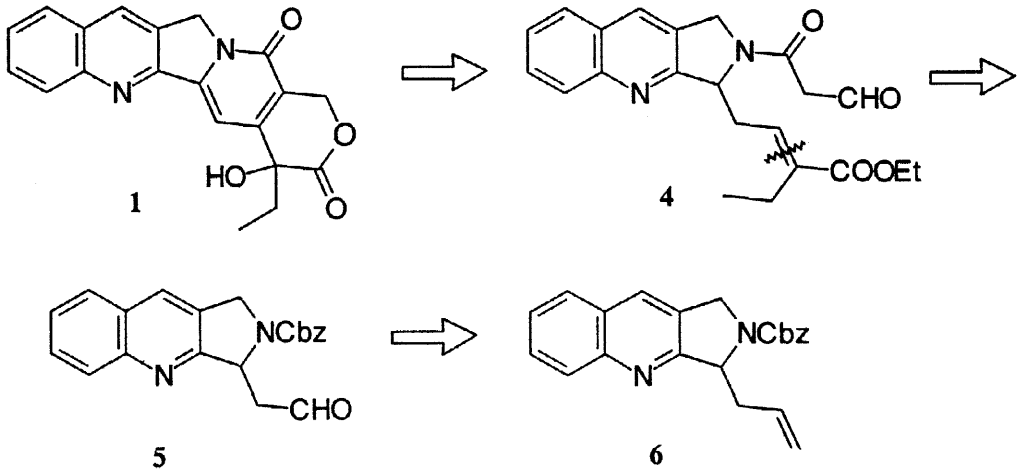
A retrosynthesis (Scheme-1) of camptothecin revealed an intramolecular Michael addition as a probable route with quinoline **6** as a key intermediate.

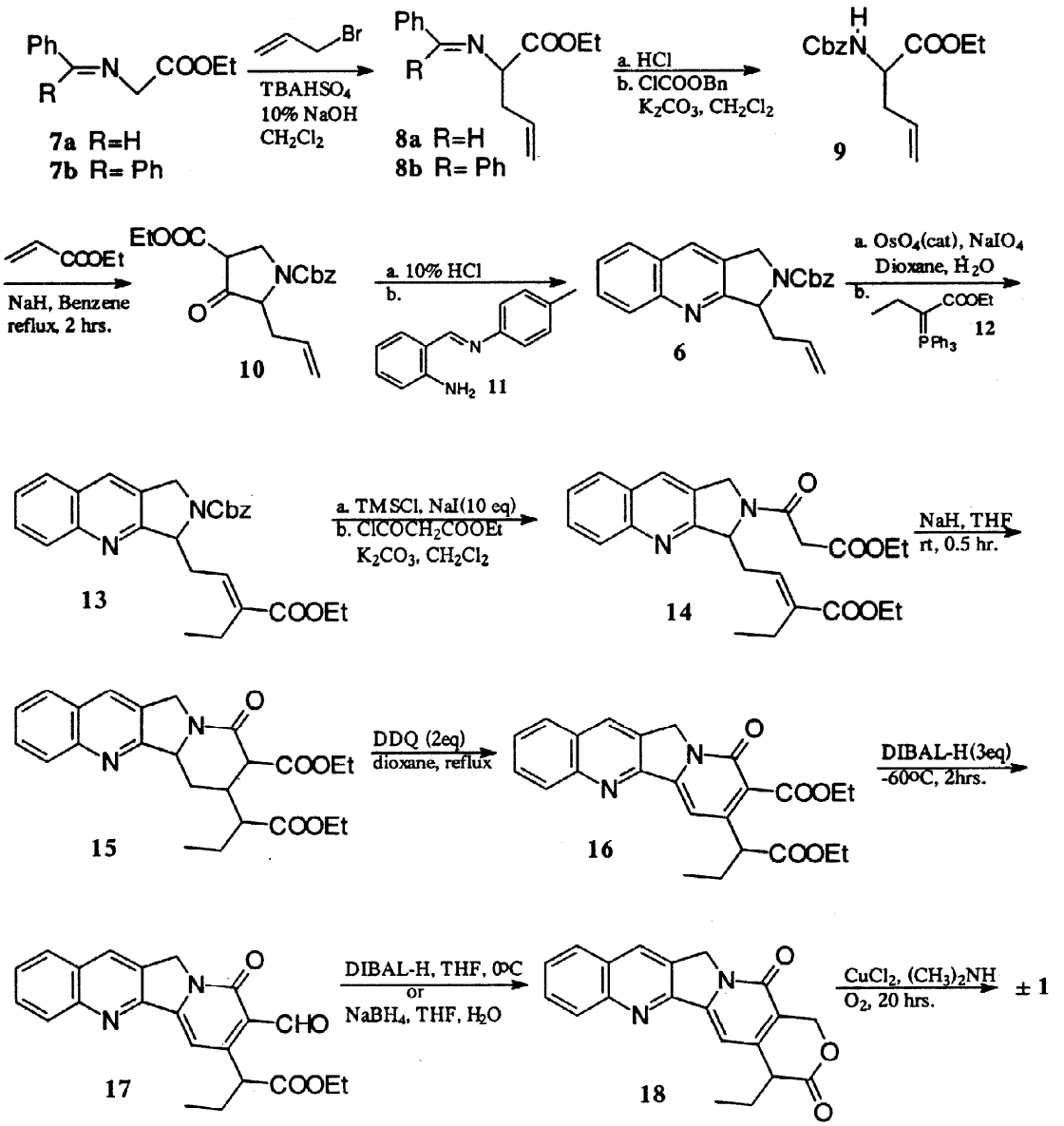


Scheme-1

The quinoline **6** was prepared starting from the Schiff's base **7a/7b**. Alkylation of **7a** and **7b** under phase transfer conditions[10,11] using tetrabutylammonium hydrogen sulfate ($TBAHSO_4$)as the catalyst and 10% aqueous NaOH as base provided the Schiff's bases **8a** and **8b** respectively in excellent yields. Hydrolysis to the amine followed by protection as a urethane gave **9** in 96% yield. Tandem Michael-Dieckmann[12] condensation using ethyl acrylate as the Michael acceptor then provided the keto ester **10** in 68% yield. Hydrolysis-decarboxylation of **10** followed by Friedlander condensation[13] with Schiff's base **11** furnished the quinoline **6** in 72% yield as a white solid.

Oxidative cleavage of the olefin **6** using $NaIO_4/OsO_4$ (cat.)[14] followed by a Wittig olefination using phosphorane **12**[15] gave the α,β-unsaturated ester **13** in 83% yield. By incorporating the ethyl functionality at this stage the problem of low yields and unselective dialkylation obtained in the other syntheses are avoided. Selective deprotection of Cbz using NaI/TMSCl (10eq.)[16] followed by condensation with carbethoxy acetyl chloride provided amide **14** in 66% yield.

Amide **14**, which has the functionalities necessary for the proposed intramolecular Michael addition[17], was treated with sodium hydride in THF at room temperature. This reaction furnished the desired tetrahydropyridone **15** in 92% yield as a mixture of diastereomers. Since the tetrahydropyridone **15** has to be oxidized and consequently the chirality of both the diastereomers will be destroyed in the next step in the synthesis of camptothecin, no attempt was made to separate them. Oxidation to pyridone **16** was accomplished in refluxing dioxane using 2 eq. of DDQ[18].



Scheme-2

Selective reduction of pyridone **16** using DIBAL-H (3 eq.)[19] at -60°C gave the aldehyde **17** as an exclusive product in 81% yield. Here selective reduction of the aromatic ester over the aliphatic ester has been achieved, eliminating the need for one ester to be a t-butyl ester. Reductive lactonization in the presence of 1 eq. DIBAL-H or $NaBH_4$ provided deoxycamptothecin **18** in excellent yields. Conversion of deoxycamptothecin **18** to camptothecin **1** was accomplished employing Danishefsky's procedure[20,21] to give 92%

yield of **1** which had identical spectral properties in all respects to those obtained from natural sources.

In conclusion, an elegant synthesis of camptothecin has been achieved in 14 steps starting from the easily available aminoacid glycine. Selective reduction of an aromatic ester in the presence of an aliphatic ester has been achieved without the need for differently protecting the esters. Incorporation of the ethyl group during the Wittig reaction eliminated the problem of dialkylation encountered during the previous synthesis. The simplicity of the reactions and mild conditions employed coupled with high efficiency makes this synthesis attractive especially from a practical viewpoint.

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[21] All the compounds were characterized by the analysis of the spectral properties(IR, ^{1}HNMR, ^{13}CMR). All new compounds gave satisfactory elemental analysis.