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ASYMMETRIC SYNTHESIS OF (S)-CAMPTOTHECIN[1]

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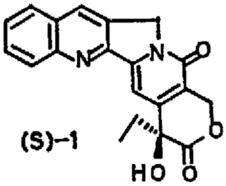
Summary: The title compound was synthesized via a novel diastereoselective ethylation process from indolizine derivative **5a** bearing N-tosyl-(R)-proline.

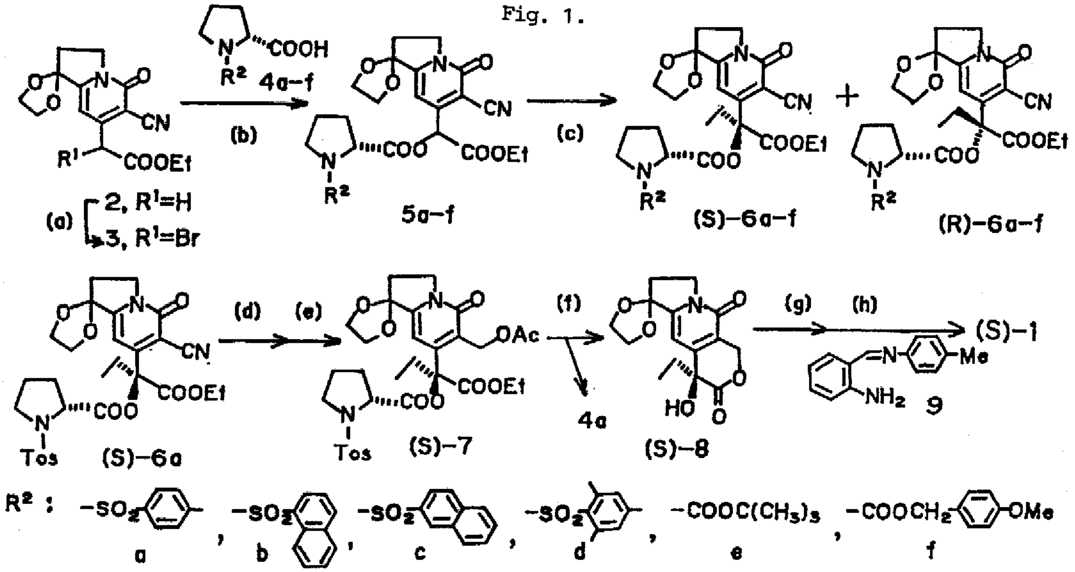
(S)-Camptothecin (**1**), a potent antitumor alkaloid, was isolated from Camptotheca acuminata (Nyssaceae) by Wall et al. in 1966,[2] and has a pentacyclic ring system containing an optically active hydroxy lactone. Synthesis of (S)-**1** via an optical resolution process has been reported by Corey et al.,[3] Wall et al.,[4] and our group.[5] In this paper we will describe a first asymmetric synthesis of (S)-**1** via a novel diastereoselective ethylation process.


(S)-1

The synthesis of (S)-**1** is outlined in Fig. 1. Our synthetic strategy involves the diastereoselective ethylation of indolizine derivatives **5a-f** using N-substituted (R)-proline as a stereocontrolling unit to the corresponding optically active (S)-**6a-f**. Diastereomers **5a-f** were prepared from the known compound **2**[6] via bromination. The ethylation was performed in 4-5 h with ethyl iodide in the presence of sodium hydride at room temperature. The results are shown in Table 1. Although no diastereoselection was observed in the reaction of **5e-f**, the ethylation of **5a-d** takes place from the side opposite to that where the aryl sulfonyl group acts as a steric hindrance, to afford (S)-**6a-d** as predominant stereoisomers. The preferred conformation of the transition state seemed to be rigid, because the diastereomeric ratio was unchanged at any of various reaction temperatures between -10°C and 60°C. This diastereoselective ethylation is an instance of 1,4-asymmetric induction, and no reports of asymmetric synthesis using N-tosyl-(R)-proline have appeared in the literature. Furthermore, optically active (S)-**6a**, bearing N-tosyl-(R)-proline, was easily isolated by treatment with 2-propanol (56% yield from **5a**).

Compound (S)-**6a** was hydrogenated, acetoxylated, hydrolyzed, and lactonized to afford optically active key intermediate (S)-**8** ($[\alpha]_D$ +109.7° (c 0.76, $CHCl_3$)). On alkaline hydrolysis, N-tosyl-(R)-proline was recovered in 66% yield without racemization. The tricyclic ketone (S)-**8** was deketalized, and condensed with compound **9**[7] to give natural (S)-**1** ($[\alpha]_D$ +42.0° (c 0.51, $CHCl_3$-MeOH,4:1); lit.[8] $[\alpha]_D$ +42.8° ($CHCl_3$-MeOH,4:1)).

Fig. 1.



(a)NaH, Br_2, DME, r.t., (85%); (b)4a-f, Na_2CO_3, DMF, 70°C, (76-97%); (c)NaH, EtI, DMF, r.t., (65-100%); (d)H_2/Raney-Ni, Ac_2O, r.t., (quant.); (e)i)$NaNO_2$, AcOH, 0°C, ii)CCl_4, reflux, (74% 2 steps); (f)i)LiOH, 67%EtOH, r.t., ii)AcOH, r.t., (90% 2 steps); (g)80%TFA, r.t., (79%); (h)9, p-TsOH, toluene, reflux, (73%).

Table 1. Diastereoselective Ethylation of 5a-f with Ethyl Iodide

Compound	Yield of 6a-f/%	Ratio (S:R)[a]
5a	~100	82 : 18
5b	94	79 : 21
5c	~100	82 : 18
5d	70	72 : 28
5e	76	51 : 49
5f	65	53 : 47

a) Determined by ^1H NMR.

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