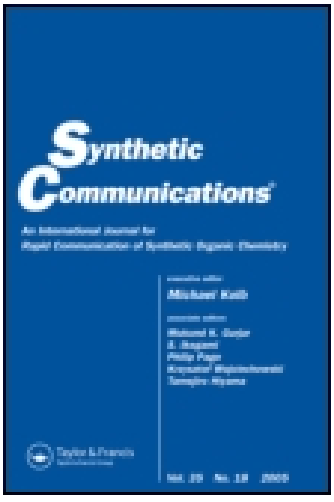

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New Route for Conversion of Camptothecin to 7-Ethylcamptothecin and 7-Propylcamptothecin

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New Route for Conversion of Camptothecin to 7-Ethylcamptothecin and 7-Propylcamptothecin

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Abstract: In this article, a new route for conversion of camptothecin to 7-ethylcamptothecin and 7-propylcamptothecin is described. Compared with previous reports, the reaction time of the new synthetic route was greatly shortened to 30 min, and the products were obtained in high yield.

Keywords: camptothecin, 7-ethylcamptothecin, high yield, new route, 7-propylcamptothecin

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INTRODUCTION

Camptothecin (CPT), a cytotoxic alkaloid first isolated from *Camptotheca acuminata* by Wall and his coworkers in 1966, was shown to have strong antitumor activity against L_{1210} leukemia and Walker 256 carcinosarcoma models.[1,2] The unique mechanism of action that camptothecin inhibits, topoisomerase I, has revived the interest in CPT and its analogues as antitumor agents.[3] A lot of analogues and derivates of CPT were prepared. Among these, Topotecan and Irinotecan received FDA approval, and some other are in clinical development.[4]

7-Ethyl-10-hydroxycamptothecin (SN-38) and 7-proply-10-hydroxycamptothecin were synthesized by Sawada et al.[5,6] SN-38 is a metabolite of Irinotecan, which undergoes deesterification in *vivo*[5] 7-Propyl-10-hydroxycomptothecin was also more potent than CPT.[6] The route of synthesizing 7-ethycamptothecin is important in the synthesis of SN-38: 7-propylcamptothecin to 7-propyl-10-hydroxycamptothecin.

According to the method of Sawada et al.[5,6] CPT was treated with $FeSO_4 \cdot 7H_2O$, CH_3CH_2CHO (or $CH_3CH_2CH_2CHO$), and H_2O_2 in H_2SO_4 to obtain the product of 7-ethylcamptothecin (or 7-propylcamptothecin). But it was pointed out by You et al.[7] that the yield was low when this method was used to synthesize 7-ethylcamptothecin.

To improve the yield, You et al. added acetic acid to obtain a homogeneous system (yield: 54%). Lei et al.[8] also studied this reaction; the yield only reached 70%. Wang et al.[9] studied the reaction of synthesizing 7-propylcamptothecin, and the product was obtained in 65% yield.

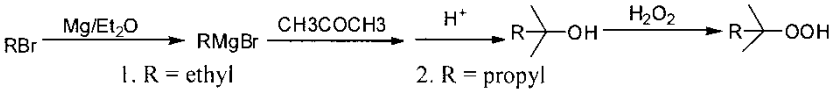
We found a new route for conversion of camptothecin to 7-ethylcamptothecin and 7-propylcamptothecin; hydroperoxide was used instead of CH_3CH_2CHO (or $CH_3CH_2CH_2CHO$) and H_2O_2. The present procedure offers several advantages including much higher yield (7-ethylcamptothecin in 83.3% and 7-propylcamptothecin in 73.6% yields), short reaction time (within 30 min to complete the reaction), and the near completeness of the reaction.

Hydroperoxide has been prepared with ordinary method as shown in Scheme 1. Then compounds **1**, **2** were used to get 7-ethylcamptothecin and 7-propylcamptothecin (Scheme 2).

EXPERIMENTAL

General Procedure

Camptothecin (0.2 g, 0.58 mmol) was suspended in a mixture of acetic acid (2.0 ml) and H_2SO_4 (0.6 ml). After several minutes, a homogeneous system was obtained. Then $FeSO_4 \cdot 7H_2O$ (0.42 g, 1.5 mmol) and H_2O (1.8 ml) were added successively. After cooling to 2°C, hydroperoxidively (0.8 ml)



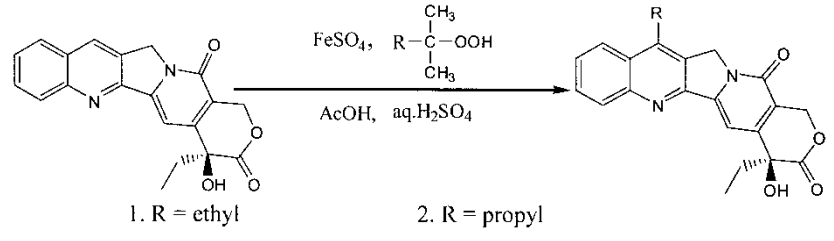
Scheme 1.

was added dropwise. The mixture was stirred for 30 min at 0°C and was then poured into ice water. The suspension was extracted with $CHCl_3$ (4 × 20 ml), and the solvent was removed under reduce pressure. The residue was purified through column chromatography of silica gel with $CHCl_3$ as elute.

Data

7-Ethylcamptothecin: Yellow powder (0.18 g), yield: 83.3%, mp: 259–261°C. IR (KBR): V_{max}: 3430, 1750, 1653, 1598 cm^{-1}. ^1H NMR ($CDCl_3$): δ: 1.03 (3H, t, $J = 6.90$ Hz, C18-methyl protons), 1.43 (3H, t, $J = 6.90$ Hz, CH_3CH_2-), 1.89 (2H, m, C19-methylene protons), 3.20 (2H, q, CH_3CH_2-), 5.26 (2H, s, C5-methylene protons), 5.28–5.77 (2H, dd, $J = 16.20$ Hz, C-17 methylene protons), 7.71 (1H, t, $J = 7.59$ Hz, C10-H), 7.82 (1H, s, C14-H), 7.80 (1H, t, $J = 7.50$ Hz, C11-H), 8.13 (1H, d, $J = 7.80$ Hz, C9-H), 8.23, (1H, d, $J = 8.10$ Hz, C12-H). Anal calcd. for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36; N, 7.44%. Found: C, 70.10; H, 5.30; N, 7.40%. HRMS (EI+): m/z calcd. for $C_{22}H_{20}N_2O_4$; 376.1423; found: 376.1419.

7-Prpylcamptothecin: Yellow power (0.165 g), yield: 73.6%, mp: 232–233°C. IR (KBr): νmax: 3430, 1745, 1650, 1600 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.88–1.13 (8H, C19-methyl protons, $CH_3CH_2CH_2-$), 1.92 (2H, m, C18-methylene protons), 3.18 (2H, t, $J = 7.56$ Hz, $CH_3CH_2CH_2-$), 5.28 (2H, s, C5-methylene protons), 5.29–5.79 (2H, dd, $J = 16.32$ Hz, C-17 methylene protons), 7.71 (1H, t, $J = 7.59$ Hz, C10-H), 7.72 (1H, s, C14-H), 7.81 (1H, t, $J = 7.29$ Hz, C11-H), 8.12 (1H, d, $J = 8.34$ Hz, C9-H), 8.26 (1H, d, $J = 8.4$ Hz, C12-H). Anal calcd. for $C_{23}H_{22}N_2O_4$: C, 70.75; H, 5.68; N,



Scheme 2.

7.18%. Found: C, 70.60; H, 5.60; N, 7.10%. HRMS (EI+): m/z calcd. for $C_{23}H_{22}N_2O_4$: 390.1580; found: 390.1587

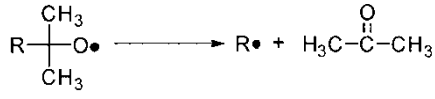
DISCUSSION

According to the literature, [8,10] alkylation in position 7 of CPT in acidic media is probably a radical mechanism.

When hydroperoxide was used with transition-metal salt, the corresponding triple-alkoxyl radicals were produced[11]

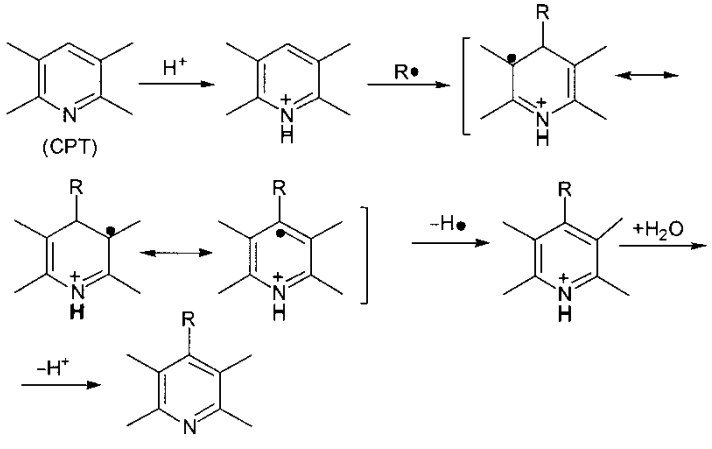
(1)

As a common fragmentation, triple-alkoxyl radical can split into alkyl radical and acetone.[12]



(2)

The ethyl (propyl) radical formed acted with CPT to generate the 7-ethylcamptothecin (7-propylcamptothecin) species as shown in 3.[8,10]



1. R = ethyl 2. R = propyl (3)

In addition, it is very important to add acetic acid to the solvent system because that will improve the solubility of CPT remarkably and accordingly result in a much higher yield. The order of adding materials and the usage of H_2SO_4 and $FeSO_4 \cdot 7H_2O$ are important too and deeply affect the reaction course. For example, when we added 0.15 g of $FeSO_4 \cdot 7H_2O$ to

the system, the yield was low. In contrast, when 0.42 g of $FeSO_4 \cdot 7H_2O$ was added to the system, the reaction finished completely.

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