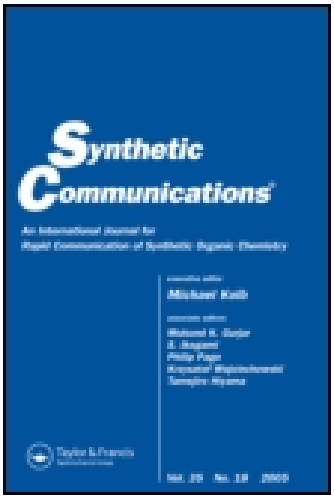

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Novel Route for Preparation of 7-Methyl-camptothecin and Its Possible Mechanism

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Published online: 20 Aug 2006.

To cite this article: Xin Wang, Jiwu Wen, Gang Li & Tianpa You (2005) Novel Route for Preparation of 7-Methyl-camptothecin and Its Possible Mechanism, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 35:24, 3163-3166

To link to this article: http://dx.doi.org/10.1080/00397910500283263

Synthetic Communications®, 35: 3163–3166, 2005

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910500283263

Novel Route for Preparation of 7-Methyl-camptothecin and Its Possible Mechanism

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Abstract: A novel route for preparation of 7-methyl-camptothecin is described. Its possible mechanism is discussed.

Keywords: Mechanism, 7-methyl-camptothecin, novel route, preparation

INTRODUCTION

Camptothecin (CPT),[1] a pentacyclic alkaloid isolated from the Chinese tree *Camptotheca acuminata* by Wall et al. in 1966, was shown to have strong antitumor activity against colon, mammary, leukemia, and ovarian tumor models. The discovery of its unique mechanism of action, trapping a cleavable complex between topoisomerase I and DNA,[2] revived the research interest in CPT and its analogs as antitumor agents. A number of CPT analogs have been developed. SAR studies had indicated that a lipophilic group in position 7 such as 7-alkyl-camptothecins are substantially more cytotoxic than CPT.[3–5] Among 7-alkyl-camptothecins, 7-methyl-camptothecin was the most potent in inhibiting tumor cell growth.[5]

7-Methyl-camptothecin was previously prepared by treatment of CPT with H_2O_2, $FeSO_4 \cdot 7H_2O$, and CH_3CHO in aq. H_2SO_4[5] in moderate yield ($<70\%$). We have found a novel route for preparation of 7-methyl-camptothecin by treatment of CPT with $FeSO_4$, $HCONH_2$, and

Received in Japan May 23, 2005
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$(CH_3)_3COOH$ under acidic conditions. The present procedure offers several advantages such as much higher yields (96.1%), easy purification of the product (do not need to use column chromatography), and fast reaction time (within 1 h to complete the reaction). This provides an alternative method.

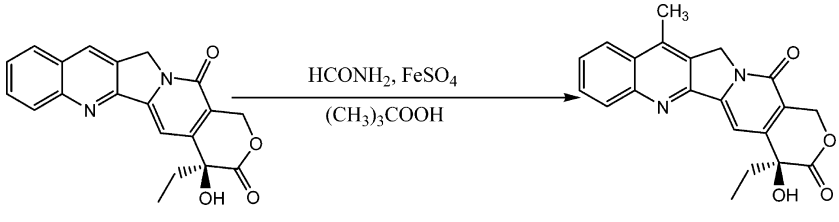
EXPERIMENTAL

Camptothecin (0.1 g, 0.29 mmol) was suspended in a mixture of CF_3COOH (3.5 ml) and H_2SO_4 (1.2 ml). $FeSO_4 \cdot 7H_2O$ (0.21 g, 0.76 mmol) and H_2O (6 ml) were added successively. After cooling to 5°C, $HCONH_2$ (0.2 ml) was added. To the mixture, 65% $(CH_3)_3COOH$ (0.1 ml, 0.68 mmol) was added dropwise at 2°C. The mixture was stirred for 1 h at 0°C and then poured into ice water. The precipitated material in the solution was collected by suction, washed with water, and dried in vacuo. Yellow powder (0.100 g) was obtained. Yield: 96.1%. IR (KBr) ν_{max}: 3430, 1750, 1653, 1602 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 0.91 (3H, t, $J = 7.20$ Hz, C18-methyl protons), 1.83–1.96 (2H, m, C19-methylene protons), 2.81 (3H, s, C7-CH_3), 5.31 (2H, s, C5-methylene protons), 5.47 (2H, s, C17-methylene protons), 7.35 (1H, s, C14-H), 7.75 (1H, t, $J = 7.36$ Hz, C10-H), 7.89 (1H, t, $J = 7.06$ Hz, C11-H), 8.17 (1H, d, $J = 8.12$ Hz, C9-H), 8.26 (1H, d, $J = 8.45$ Hz, C12-H). Anal. calcd. for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.01; N, 7.73%. Found: C, 69.40; H, 4.75; N, 7.58%. HRMS (EI) m/z calcd. for $C_{21}H_{18}N_2O_4$: 362.127; found: 362.129.

DISCUSSION

According to the literature,[6,7] methylation in the 7 position of CPT in acidic media is presumably a radical mechanism.

The only possible source of methyl radical in Scheme 1 must come from *t*-butyl hydroperoxide. As Richardson had pointed out,[8] when *t*-butyl



Scheme 1.

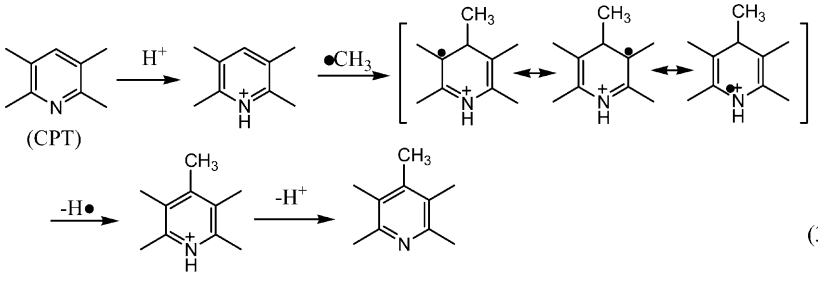
hydroperoxide was used with transition-metal salt, a *t*-butoxy radical was usually produced.

$$Fe^{2+} + (CH_3)_3COOH \longrightarrow Fe(OH)^{2+} + (CH_3)_3CO\bullet \quad (1)$$

As a common fragmentation, *t*-butoxy radical split into methyl radical and acetone:[9]

$$(CH_3)_3CO\bullet \longrightarrow \bullet CH_3 + (CH_3)_2CO \quad (2)$$

The methyl radical acted with CPT to afford the methylated species as shown in reaction (3):[6,7]



(3)

It is important to add CF_3COOH to the solvent system because that remarkably improves the solubility of CPT and results in high yield. However, the function of $HCONH_2$ remained unknown. The fact is that no target product is obtained without the assistance of $HCONH_2$. We think the function of $HCONH_2$ may be to stabilize the methyl radical.

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