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Chemical Modification of an Antitumor Alkaloid Camptothecin: Synthesis and Antitumor Activity of 7-*C*-Substituted Camptothecins

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A radical substitution reaction of 20(*S*)-camptothecin (1) with methanol furnished 7-hydroxymethylcamptothecin (2). Reaction of 1 with primary alcohols higher than methanol gave 7-alkylcamptothecins (4), of which alkyl groups were one carbon less than the alcohols used and also 7-hydroxyalkylcamptothecins (5). For the preparation of 7-alkylcamptothecin (4), aldehydes were used as a radical source and several alkylated derivatives were synthesized. 7-Acyloxymethyl derivatives (6), 7-carbaldehyde (7), iminomethyl derivatives (10), acid (11), esters (12) and amides (13) were synthesized starting from 2. 7-Ethyl- (4b) and 7-propylcamptothecin (4c), acyloxymethyl compounds 6a, 6c and ethyl ester (12b) exhibited higher antitumor activity than 1 against L1210 in mice.

Keywords 20(*S*)-camptothecin; homolytic alkylation; 7-alkylcamptothecin; 7-hydroxymethylcamptothecin; 7-ethylcamptothecin; 5-*O*-substituted camptothecin; antitumor activity; leukemia L1210

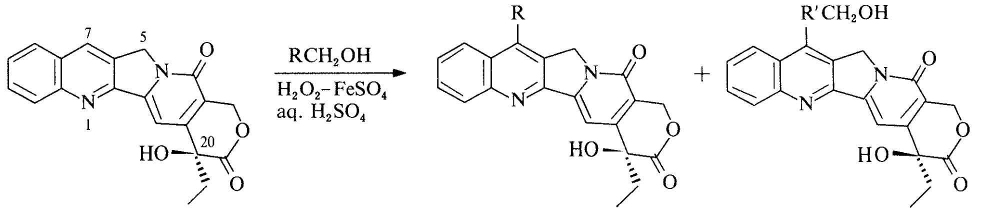
20(*S*)-Camptothecin (**1**) is an alkaloid which was first isolated from *Camptotheca acuminata* (Nyssaceae) by Wall and co-workers in 1966.[1)] It has attracted much attention because of its significant antitumor activity in various murine tumor systems. In clinical trials, however, the high toxicity of this alkaloid has restricted its therapeutic usefulness.[2)]

We have been conducting a study on chemical modification of **1** to obtain derivatives with less toxicity.[3)] We wish to report here the synthesis of 7-*C*-substituted camptothecins and their antitumor activities against leukemia L1210 in mice.

Chemistry As pointed out by Minisci and Porta, homolytic alkylation of heteroaromatic bases can be performed in aqueous acidic media: alkyl radicals add at the electron-deficient positions of the protonated bases.[4)] Treatment of **1** with hydrogen peroxide and ferrous sulfate in an aqueous methanol–sulfuric acid solution furnished 7-hydroxymethylcamptothecin (**2**) in 82% yield. The formation of **2** was also observed by heating **1** with hydroxylamine-*O*-sulfonic acid (HSA)[5)] as a suspension in aqueous methanol or with ammonium persulfate in a mixture of methanol–sulfuric acid.[4)] But in the latter cases the yields were low. Application of homolytic reaction using glycolic acid and ammonium persulfate in the presence of silver ion[6)] resulted in the formation of 5-hydroxycamptothecin (**3a**, 10% yield) in addition to **2** (19% yield) and trace amounts of camptothecin 1-oxide.

We also examined the radical substitution reaction of **1** with primary alcohols such as ethanol, propanol, butanol and isobutanol. The predominant product of the reaction was 7-alkylcamptothecins (**4**), of which the alkyl groups were one carbon less than the alcohols used having lost the carbinol moiety. 7-Hydroxyalkylcamptothecins (**5**) were also formed by this reaction. Displacement reaction of the hydrogen atom of the alcohols was observed at each position except for the α- and tertiary carbon. For example, using ethanol as a radical source, two products were isolated

TABLE I. Results of the Homolytic Reactions of **1** with Primary Alcohols Yielding 7-Alkyl- (**4**) and 7-Hydroxyalkylcamptothecins (**5**)



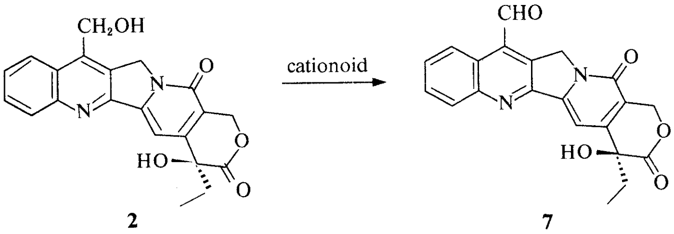
1: 20(*S*)-camptothecin **4** **5**

Alcohol	4	R	Yield (%)	5	R'CH₂OH	Yield (%)
CH_3CH_2OH	a	$-CH_3$	40	a	$-CH_2CH_2OH$	32
$CH_3CH_2CH_2OH$	b	$-C_2H_5$	40	b	$-CH(CH_3)CH_2OH$	22
				c	$-CH_2CH_2CH_2OH$	12
$CH_3CH_2CH_2CH_2OH$	c	$-C_3H_7$	35	d	$-CH(C_2H_5)CH_2OH$	20
				e	$-CH(CH_3)CH_2CH_2OH$	15
				f	$-CH_2CH_2CH_2CH_2OH$	5
$(CH_3)_2CHCH_2OH$	d	$-CH(CH_3)_2$	48	g	$-CH_2CH(CH_3)CH_2OH$	12
$(CH_3)_2CHCH_2CH_2OH$	e	$-CH_2CH(CH_3)_2$	8	h	$-CH_2CH(CH_3)CH_2CH_2OH$	15
$CH_3(CH_2)_3CH_2OH$	f	$-C_4H_9$	9		Not isolated	
$C_6H_5CH_2CH_2OH$	g	$-CH_2C_6H_5$	33		Not isolated	
$C_6H_5CH_2CH_2CH_2OH$	h	$-CH_2CH_2C_6H_5$	14		Not isolated	
Cyclic-$C_6H_{11}CH_2OH$	i	-cyclic-C_6H_{11}	23		Not isolated	

TABLE II. Preparation of 7-Alkylcamptothecins (**4**) by the Reaction of **1** with Aldehydes

Aldehyde	Product	R	Yield (%)
C_2H_5CHO	**4b**	$-C_2H_5$	77
C_3H_7CHO	**4c**	$-C_3H_7$	60
C_4H_9CHO	**4f**	$-C_4H_9$	48
$C_6H_5CH_2CHO$	**4g**	$-CH_2C_6H_5$	51
n-$C_7H_{15}CHO$	**4j**	$-C_7H_{15}$	38

TABLE III. Synthesis of Aldehyde (**7**) by the Reaction of **2** with Cationoid Reagents



Cationoid	Solvent	Temp (°C)	Time (h)	Yield (%)
H_2SO_4	H_2O	Reflux	30.5	30
CH_3COOH	Neat	Reflux	5.5	68
$BF_3\cdot OEt_2$	TCE[a]–dioxane	Reflux	14.5	26
$POCl_3$	$CHCl_3$–dioxane	Reflux	2.0	34
$SOCl_2$	$CHCl_3$–dioxane	Reflux	14.5	57
TsCl[b]	Pyridine	80—90	4.5	69
Ph_3P–CCl_4	DMF[c]	80—90	10.0	56

a) Tetrachloroethane. *b*) *p*-Toluenesulfonyl chloride. *c*) *N*,*N*-Dimethylformamide.

through silica gel column chromatography. The compound with a higher *Rf* value on thin layer chromatography (TLC) was 7-methylcamptothecin (**4a**), and the other was 7-(2-hydroxyethyl)camptothecin (**5a**); they were obtained in 40% and 32% yields, respectively.[7] In the case of propanol, three products were obtained in a similar manner; the compound with the highest *Rf* value was 7-ethyl derivative (**4b**) and the others were 7-(1-hydroxy-2-propyl)- and 7-(3-hydroxy-1-propyl)camptothecins (**5b** and **5c**).

In the case of pentanol or higher alcohols, 7-alkyl derivatives were isolated in lower yields due to poor solubility of the alcohols in the reaction medium. The 7-hydroxyalkyl derivatives could not be isolated from the complex mixtures.

Attempted synthesis of 7-*tert*-butyl derivative using 2,2-dimethylpropanol furnished only 7-methylcamptothecin (**4a**) in a low yield. The reaction with secondary alcohol such as isopropanol gave small amounts of **4a** and 7-(2-hydroxy-1-propyl)camptothecin (**5i**) in 11% yield.

7-Methylcamptothecin (**4a**) was produced in 79% yield by the reaction with *tert*-butylhydroperoxide as the radical source in the presence of ferrous ion.[4] For the preparation of 7-ethylcamptothecin (**4b**), we examined the use of propionaldehyde, diethylketone and propionic acid as the radical source.[8] The best result was obtained with the aldehyde (77% yield), on the other hand the reactions with the ketone and the acid afforded **4b** in 22% and 13% yields, respectively, together with a complex mixture. Further examples of the alkylation of **1** using aldehydes are presented in Table II.

As the reaction mechanism, for example with propanol, it was speculated that the alcohol yields a propoxy radical and three possible carbon radicals (α, β and γ position) by the action of the hydroxyl radical formed under the conditions. The propoxy radical undergoes self-decomposition to the more reactive ethyl radical. In the reaction, 7-ethyl (**4b**) and hydroxyalkyl compounds (**5b** from the β-radical, **5c** from the γ-radical) were isolated, but not the product of the α-radical, probably due to its reduced reactivity (stabilized by the α-oxygen).[4] With branched alcohols such as 2-methylpropanol and 3-methylbutanol, the tertiary radicals did not attack **1** possibly due to steric reasons. The aldehydes afford the corresponding ketyl radicals by the action of the hydroxyl radical, which decompose to alkyl radicals and carbon monoxide, and then the alkylation reactions occur predominantly to give 7-alkyl compounds (**4**).

We synthesized various 7-*C*-substituted derivatives starting from 7-hydroxymethylcamptothecin (**2**). Acylation of **2** with acid anhydride gave the acyloxymethyl compound (**6**) in good yield, whereas acid chlorides such as benzoyl and phenylacetyl chlorides afforded 7-formylcamptothecin (**7**) in addition to the corresponding acyloxymethyl compounds (**6**). The treatment with *p*-toluenesulfonyl chloride in hot pyridine and with the chlorinating agents showed in Table III effected the conversion of **2** to **7**. Compound **2** was also converted into **7** by heating in aqueous sulfuric or acetic acid.

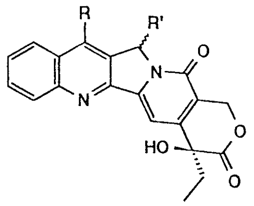
Heating of **2** in methanol or ethanol in the presence of 15% (v/v) sulfuric acid furnished ethers (**8a**, 38.6%, **8b**, 20.7%) and acetals (**9a**, 17%, **9b**, 16%), the latter being hydrolyzed into **7**. By heating in butanol containing 15% (v/v) sulfuric acid, **2** was converted into 7-butoxymethyl derivative (**8c**) in 42% yield. When **2** was treated with 0.2% (v/v) sulfuric acid, 7-dibutoxymethyl derivative (**9c**) was obtained in 39% yield as the major product.

Aldehyde **7** was converted into the iminomethyl derivative (**10**) by reaction with carbonyl reagents in a mixture of ethanol–pyridine.

Chromic acid oxidation of **2** furnished carboxylic acid (**11**) in good yield. Esterification of **11** in methanol in the presence of sulfuric acid resulted in the formation of the ester in poor yield in spite of heating for a long period of time, whereas, treatment of the potassium salt of the acid with alkylating agents gave esters (**12**) in good yields.

Carboxamides, **13**, were synthesized from **11** with amines by using ethyl chloroformate and dicyclohexylcarbodiimide (DCC) as condensing agents. Aminolysis of methyl ester (**12a**) with diethylamine resulted in the formation of the acid (**11**).

Several 5-*O*-substituted camptothecins were prepared. Compound **3a** was conveniently obtained by oxidation of **1** with iodine in the presence of potassium carbonate in *N*,*N*-dimethylformamide (DMF). The nuclear magnetic resonance (NMR) spectrum suggested that **3a** was a mixture (1 : 1) of the diastereomers with respect to the configuration at the C-5. By heating in methanol and in butanol with boron trifluoride etherate, the hemiaminal, **3a**, was converted into the 5-methoxyl or 5-butoxyl derivatives (**3b** and **3c**), respectively. 5-Acyloxyl derivatives **3d** and **3e** were



3, 6, 8—13

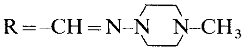
3a:	R = –H	R′ = –OH
3b:	R = –H	R′ = –OCH_3
3c:	R = –H	R′ = –OC_4H_9
3d:	R = –H	R′ = –$OCOCH_3$
3e:	R = –H	R′ = –$OCOC_6H_5$
6a:	R = –CH_2OCOCH_3	R′ = –H
6b:	R = –$CH_2OCOC_2H_5$	R′ = –H
6c:	R = –$CH_2OCOC_3H_7$	R′ = –H
6d:	R = –$CH_2OCOC_4H_9$	R′ = –H
6e:	R = –$CH_2OCOCH_2C_6H_5$	R′ = –H
6f:	R = –$CH_2OCOC_6H_5$	R′ = –H
8a:	R = –CH_2OCH_3	R′ = –H
8b:	R = –$CH_2OC_2H_5$	R′ = –H
8c:	R = –$CH_2OC_4H_9$	R′ = –H
9a:	R = –$CH(OCH_3)_2$	R′ = –H
9b:	R = –$CH(OC_2H_5)_2$	R′ = –H
9c:	R = –$CH(OC_4H_9)_2$	R′ = –H
10a:	R = –CH = N–OH	R′ = –H
10b:	R = –CH = N–NH_2	R′ = –H
10c:	R = –CH = N–$NHCH_3$	R′ = –H
10d:	R = –CH = N–NHC_6H_5	R′ = –H
10e:		R′ = –H
10f:	R = –CH = N–$NHCONH_2$	R′ = –H
11:	R = –COOH	R′ = –H
12a:	R = –$COOCH_3$	R′ = –H
12b:	R = –$COOC_2H_5$	R′ = –H
12c:	R = –$COOCH_2C_6H_5$	R′ = –H
13a:	R = –$CONH_2$	R′ = –H
13b:	R = –$CONHC_2H_5$	R′ = –H
13c:	R = –$CONHCH_2C_6H_5$	R′ = –H
13d:	R = –$CON(CH_3)_2$	R′ = –H
13e:	R = –CONH-cyclic C_6H_{11}	R′ = –H

Chart 1

prepared by the ordinary method. The diastereomers of **3d** were separated and characterized (Experimental).

Results and Discussion

The antitumor activities of the derivatives synthesized herein are presented in Table IV, compared with camptothecin (**1**). 7-Alkyl derivatives **4b** and **4c**, 7-acyloxymethylcamptothecins (**6a** and **6c**) and ethyl ester (**12b**) exhibited higher antitumor activity than **1**. In the 7-alkylcamptothecin series, 7-ethylcamptothecin (**4b**) showed 453 T/C% with 9 cured mice in 10 tested mice. The highest activity observed was in the derivative with the ethyl substituent and the compounds having lower or higher alkyl substituents than these which resulted in a decrease or loss of activity. The derivatives possessing α-branched alkyl groups (such as **4e**, **4f** and **5e**) had no activity.

Water-soluble derivatives, **10e** (as HCl salt) or **11** (as Na salt) showed slight activity. Neither the carboxamides, **13**, nor 5-*O*-substituted camptothecins, **3**, had any activity.

In general, more hydrophilic substituents caused a decrease of activity while the derivatives with more lipophilic substituents showed higher activity.

Table IV. Antitumor Activity of 7-*C*- and 5-*O*-Substituted Camptothecin Derivatives (L1210 in Mice)

Compd. No.	T/C%[a] Total dose (mg/kg) 10	25	40
1	180	313 (4/10)[b]	120
2	NT[c]	163	92
3a	92	99	102
3b	102	NT	98
3c	NT	89	98
3d	NT	101	98
3e	NT	102	99
4a	NT	160	61[e]
4b	182	453 (9/10)	81[e]
4c	182	326 (4/10)	82[e]
4d	NT	76	74[e]
4f	110	116	76[e]
4h	120	176	120[e]
5b	NT	77	76[e]
5e	NT	77	77[e]
6a	136	390 (4/10)	78
6b	NT	202 (2/10)	76
6c	136	390 (4/10)	77
6d	126	235	159
6e	NT	168	99
6f	NT	160	224 (1/10)
7	136	302 (5/10)	285
8a	320 (1/6)[d]	NT	80[e]
8b	120[d]	NT	80[e]
8c	120[d]	NT	160[e]
9a	148	129	75
9b	127	199 (1/10)	86
10a	NT	212 (1/10)	242
10b	128	182	134
10e[f]	145	185	113
11[g]	121	126	128
12a	NT	173	161 (2/10)
12b	162	340 (4/10)	76
12c	NT	115	162
12d	NT	127	131
13a	100	102	106
13b	NT	100	102
13c	NT	100	102
13d	NT	99	110

a) T/C% = (the mean survival time of treated mice)/(the mean survival time of untreated control mice). *b*) Figures in parentheses indicate (number of cured mice/number of tested mice). *c*) NT: not tested. *d*) 12.5 mg/kg. *e*) 50 mg/kg. *f*) Administerd as HCl salt in saline. *g*) Administered as Na salt in saline.

Significant antitumor activity was already reported for the 7-ethyl derivative, **4b**, in other experimental systems.[9] Further modification, for example introduction of substituents into the A-ring of **4b**, will be published elsewhere in the near future.[10]

Experimental

All the melting points (with decomposition) are uncorrected. Infrared (IR) spectra were determined on a JASCO DIR-40 spectrometer. ^{1}H-NMR spectra were measured on a JEOL JNM-FX 100 (99.6 MHz) with tetramethylsilane (TMS) as the internal standard. Mass spectra (MS) and Ultraviolet (UV) spectra were recorded on a JEOL JMS-DX 300 mass spectrometer and on a Shimadzu DIP-140 spectrophotometer, respectively. Optical rotation values were obtained with a JASCO DIP-140 spectrometer.

7-Hydroxymethylcamptothecin (2) To a suspension of **1** (3.00 g, 8.6 mmol) in a mixture of MeOH (90 ml) and H_2O (75 ml), 75% H_2SO_4 (75 ml) was added dropwise, and then $FeSO_4 \cdot 7H_2O$ (2.40 g, 8.6 mmol) was added. To the ice-cold mixture, 30% H_2O_2 (15 ml, 6.6 mmol) was added dropwise for 2 h with stirring. The mixture was stirred at room temperature for 14 h and then diluted with H_2O, the precipitate was collected on a celite pad by suction. The pad was eluted with hot DMF and the eluent was evaporated to dryness, and the residue was recrystallized to give **2** (2.70 g, 82% yield) as pale yellow prisms. mp 274—276 °C (pyridine). IR (KBr) ν: 1770, 1665, 1605 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.89 (3H, t, J=7 Hz), 1.88 (2H, q, J=7 Hz), 5.27 (2H, d, J=4 Hz, 7-C$\underline{H}_2$OH), 5.40 (2H, s, C$_5$-$\underline{H}_2$), 5.80 (2H, s, C$_{17}$-$\underline{H}_2$), 5.80 (1H, t, J=4 Hz, 7-CH$_2$O$\underline{H}$), 6.50 (1H, s, 20-O$\underline{H}$), 7.33 (1H, s, C$_{14}$-$\underline{H}$), 7.60—8.21 (4H, m, arom). MS m/z: 378.1283 (M$^+$). Calcd for $C_{21}H_{18}N_2O_5$: 378.1209. *Anal.* Calcd for $C_{21}H_{18}N_2O_5$: C, 66.66; H, 4.79; N, 7.40. Found: C, 66.02; H, 4.61; N, 7.57.

Preparation of 2 with HSA To a suspension of **1** (100 mg, 0.287 mmol) in MeOH (200 ml), HSA (100 mg, 0.881 mmol) was added. The mixture was heated for 36 h while adding HSA (100 mg, 0.881 mmol) every 3 h during heating. The insoluble material was collected by suction and dissolved in a mixture of DMF–pyridine (1 : 1, 50 ml). To the solution, acetic anhydride (300 mg, 2.94 mmol) was added. The mixture was warmed at 70—80 °C for 18 h and then evaporated to dryness. The residue was dissolved in $CHCl_3$ (200 ml) and washed with an aqueous NaCl solution. The organic layer was separated and dried over $MgSO_4$, filtered and evaporated. The residue was purified through silica gel column chromatography with $CHCl_3$. The combined fractions containing 7-acetoxymethyl-20-*O*-acetylcamptothecin were evaporated to dryness. The residue was dissolved in MeOH (20 ml) containing 1 N NaOH (10 ml) and the mixture was heated at 70—80 °C for 18 h. The mixture was condensed and then the residue was acidified with 1 N HCl (10 ml). The precipitate was collected and washed with acetone (10 ml) to give **2** (32 mg, 28.7% yield).

Preparation of 2 with $(NH_4)_2S_2O_8$ To a suspension of **1** (100 mg, 0.287 mmol) in MeOH (25 ml), 75% H_2SO_4 (10 ml) was added in an ice-bath. To the mixture an aqueous solution of $(NH_4)_2S_2O_8$ (15 g, 65.7 mmol, in 100 ml H_2O) was added dropwise over 2 h while heating at 100—110 °C. The mixture was diluted with ice-H_2O (100 ml) and the precipitate was extracted with a 1 : 1 mixture of $CHCl_3$–dioxane (500 ml) and then $CHCl_3$ (100 ml × 3). The combined extracts were dried over $MgSO_4$, filtered, and evaporated to dryness. The residue was dissolved in MeOH (200 ml) at 50—60 °C. The insoluble material was filtered out by suction and the filtrate was evaporated to dryness. The residue was crystallized from DMF–dioxane to give **2** (40 mg, 36.9% yield).

Preparation of 2 Using Glycolic Acid To a solution of **1** (50 mg, 0.143 mmol) in 75% H_2SO_4 (3 ml) containing glycolic acid (500 mg, 6.57 mmol) and silver nitrate (250 mg, 1.13 mmol), an aqueous solution of $(NH_4)_2S_2O_8$ (3 g, 13.1 mmol, in 15 ml H_2O) was added dropwise over 2 h while heating at 100—110 °C. The mixture was diluted with ice-H_2O (100 ml) and the precipitate was extracted with $CHCl_3$ (100 ml × 3). The combined extracts were dried over $MgSO_4$, filtered, and evaporated to dryness. The residue was purified by preparative TLC with 5% MeOH–$CHCl_3$ to give **2** (10.3 mg, 19.0% yield), **3a** (5 mg, 10% yield) and camptothecin 1-oxide which was identified with a synthetic sample. The *N*-oxide was obtained by the following method: A solution of **1** (3.0 g) in acetic acid (800 ml) containing 30% H_2O_2 (50 ml) was heated at 70—80 °C for 3.5 h. The mixture was condensed at 45—55 °C to about one-third, and the residue was poured into ice-H_2O (3 l). The precipitate was collected by suction. The solid was purified by recrystallization. Camptothecin 1-oxide: Yield 90.6%. Yellow-orange needles, mp 254 °C ($CHCl_3$–*n*-C_6H_{14}). IR (KBr) ν: 1745, 1645, 1590 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.88 (3H, t, J=7 Hz), 1.87 (2H, q, J=7 Hz), 5.28 (2H, s), 5.42 (2H, s), 6.51 (1H, s), 7.78—7.97 (2H, m), 8.09 (1H, s), 8.17—8.23 (2H, m), 8.63 (1H, dd, J=2, 8 Hz). MS m/z: 364 (M$^+$).

5-Hydroxycamptothecin (3a) To a solution of **1** (1.17 g, 3.7 mmol) and K_2CO_3 (556 mg, 4.0 mmol) in DMF (300 ml), I_2 (930 mg, 4.0 mmol) was added. After stirring at room temperature for 4 h, the mixture was passed through a celite pad by suction. The filtrate was evaporated to dryness, and the residue was recrystallized to give **3a** (1.03 g, 84% yield) as colorless prisms. mp 232—234 °C (acetone). IR (KBr) ν: 1743, 1655, 1597 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.89 (3H, t, J=7 Hz), 1.88 (2H, q, J=7 Hz), 5.41 (2H, br s), 6.90 (0.5H, s), 6.98 (0.5H, s), 7.21 (0.5H, s), 7.24 (0.5H, s), 7.65—8.21 (5H, m), 8.66 (1H, s, C$_7$-H). MS m/z: 364.1041 (M$^+$). Calcd for $C_{20}H_{16}N_2O_5$: 364.1053.

5-Methoxycamptothecin (3b) A solution of **3a** (224 mg, 0.62 mmol) in MeOH (40 ml) containing $BF_3 \cdot OEt_2$ (515 mg, 3.4 mmol) was heated under reflux for 6 h. The mixture was condensed, and the residue was purified through silica gel column chromatography with $CHCl_3$ to give **3b** (153 mg, 79% yield) as pale yellow needles. mp 255 °C ($CHCl_3$–*n*-C_6H_{14}). IR (KBr) ν: 1750, 1660, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.02 (3H, t, J=8 Hz), 1.92 (2H, q, J=8 Hz), 3.52 (1.5H, s, 5-OMe), 3.68 (1.5H, s, 5-OMe), 5.32 (1H, d, J=19 Hz), 5.72 (1H, d, J=19 Hz), 6.72 (0.5H, s, C$_5$-H), 6.89 (0.5H, s, C$_5$-H), 7.60 (1H, br), 7.50—8.40 (4H, m), 8.41 (1H, s). MS m/z: 387.1214 (M$^+$). Calcd for $C_{21}H_{18}N_2O_5$: 378.1209.

5-Butoxycamptothecin (3c) A solution of **3a** (224 mg, 0.62 mmol) in butanol (40 ml) containing $BF_3 \cdot OEt_2$ (515 mg, 6.4 mmol) was refluxed for 6 h. The mixture was worked up as described above to afford **3c** (170 mg, 66% yield) as pale yellow needles. mp 245 °C ($CHCl_3$–*n*-C_6H_{14}). IR (KBr) ν: 1765, 1670, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.02 (3H, t, J=8 Hz), 0.86—1.80 (7H, br m), 4.00 (4H, m), 5.22 (1H, d, J=18 Hz), 5.69 (1H, d, J=18 Hz), 6.77 (0.5H, s), 6.87 (0.5H, s), 7.33—8.40 (4H, m), 7.61 (1H, s), 8.41 (1H, s). MS m/z: 420 (M$^+$).

5-Acetoxycamptothecin (3d) To a solution of **3a** (300 mg, 0.82 mmol) in pyridine (20 ml), acetic anhydride (105 mg, 1.0 mmol) was added dropwise. The mixture was stirred at room temperature for 3 h and then evaporated to dryness. The residue was purified with preparative high performance liquid chromatography (HPLC) (Richrosorb SI-60 column, 0.5% MeOH–$CHCl_3$). **3d-1**: Yield 41%. Colorless needles, mp 202—205 °C ($CHCl_3$–*n*-C_6H_{14}). IR (KBr) ν: 1760, 1670, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.06 (3H, t, J=7 Hz), 1.90 (2H, q, J=7 Hz), 2.195 (3H, s), 5.22 (1H, d, J=16 Hz), 5.64 (1H, d, J=16 Hz), 7.62 (1H, s), 7.91 (1H, s), 7.68—8.26 (4H, m), 8.45 (1H, s). MS m/z: 406.1176 (M$^+$). Calcd for $C_{22}H_{18}N_2O_6$: 406.1158. $[\alpha]_D^{25}$ +117.3° (c=0.0052, pyridine). **3d-2**: Yield 36%. Pale yellow needles, mp 258—261 °C ($CHCl_3$–*n*-C_6H_{14}). IR (KBr) ν: 1760, 1670, 1625, 1595 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, t, J=7 Hz), 1.90 (2H, q, J=7 Hz), 2.192 (3H, s), 5.22 (1H, d, J=17 Hz), 5.67 (1H, d, J=17 Hz), 7.62 (1H, s), 7.96 (1H, s), 7.70—8.30 (4H, m), 8.46 (1H, s). MS m/z: 406.1134 (M$^+$). Calcd for $C_{22}H_{18}N_2O_6$: 406.1158. $[\alpha]_D^{25}$ −123° (c=0.0033, pyridine).

5-Benzoyloxycamptothecin (3e) Yield 68%. Pale yellow needles, mp 260 °C ($CHCl_3$–*n*-C_6H_{14}). IR (KBr) ν: 1760, 1740, 1670, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.02 (3H, t, J=7 Hz), 2.00 (2H, q, J=7 Hz), 5.23 (1H, d, J=18 Hz), 5.56 (1H, d, J=18 Hz), 7.33—8.40 (9H, m), 7.21 (0.5H, s), 7.32 (0.5H, s), 8.72 (1H, s). MS m/z: 468.1296 (M$^+$). Calcd for $C_{27}H_{20}N_2O_6$: 468.1314.

Reaction of 1 with Alcohols or Aldehydes, General Procedure To a suspension of **1** (1.00 g, 2.9 mmol) containing $FeSO_4 \cdot 7H_2O$ (300 mg, 1.1 mmol) and an alcohol or aldehyde (2 ml) in H_2O (20 ml), conc. H_2SO_4 (11 ml) was added dropwise. To the mixture 30% H_2O_2 (720 mg, 6.4 mmol) was added dropwise with stirring in an ice-salt bath. The mixture was stirred at room temperature for 3 h and then diluted with H_2O. The precipitate was extracted with $CHCl_3$ (100 ml × 3). The combined extracts were evaporated, and the residue was passed through silica gel column chromatography with 2% MeOH–$CHCl_3$.

4a: Pale yellow needles, mp 280—281 °C (pyridine–MeOH). IR (KBr) ν: 1755, 1650, 1600 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.91 (3H, t, J=8 Hz), 1.88 (2H, q, J=8 Hz), 2.79 (3H, s), 5.26 (2H, s), 5.41 (2H, s), 6.43 (1H, s), 7.34 (1H, s), 7.57—8.32 (4H, m). MS m/z: 362 (M$^+$). *Anal.* Calcd for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.00; N, 7.73. Found: C, 69.42; H, 4.92; N, 7.76.

Preparation of 4a Using *tert*-Butylhydroperoxide To a suspension of **1** (500 mg, 1.43 mmol) in H_2O (15 ml) containing $FeSO_4 \cdot 7H_2O$ (150 mg, 0.55 mmol) and AcOH (1.5 ml), conc. H_2SO_4 (8 ml) was added dropwise, and then *tert*-butylhydroperoxide (900 mg, 10.0 mmol) was added dropwise with stirring in an ice-salt bath. The mixture was stirred at room temperature for 1 h and then diluted with H_2O. The precipitate was extracted with $CHCl_3$ (1.5 l). The extract was evaporated, and the residue was washed with acetone and then recrystallized to give **4a** (409 mg, 79.0% yield).

4b: Pale yellow needles, mp 258—261 °C ($CHCl_3$–*n*-C_6H_{14}). IR (KBr) ν: 1750, 1650, 1595 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.97 (3H, t, J=7 Hz), 1.39 (3H, t, J=7 Hz), 1.91 (2H, q, J=7 Hz), 3.21 (2H, q, J=7 Hz), 5.21 (2H, s), 5.24 (1H, d, J=16 Hz), 5.57 (1H, d, J=16 Hz), 7.49 (1H, s), 7.44—8.21 (4H, m). MS m/z: 376.1399 (M$^+$). Calcd for $C_{22}H_{20}N_2O_4$: 376.1422. *Anal.* Calcd for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36; N, 7.44. Found: C, 70.37; H, 5.35; N, 7.39.

Preparation of 4b Using Diethylketone To a suspension of **1** (1.00 g, 2.9 mmol) in H_2O (20 ml) containing $FeSO_4 \cdot 7H_2O$ (300 mg, 1.1 mmol), AcOH (15 ml) and diethyl ketone (1.29 g, 15 mmol), conc. H_2SO_4 (11 ml) was added dropwise. To the mixture 30% H_2O_2 (720 mg, 6.4 mmol) was added dropwise with stirring in an ice-bath. The mixture was stirred at room temperature for 48 h and then diluted with H_2O. The precipitate was extracted with $CHCl_3$ (100 ml × 3). The combined extracts were evaporated, and the residue was passed through silica gel column chromatography with $CHCl_3$ to give **4b** (24 mg, 22% yield).

Preparation of 4b Using Propionic Acid To a suspension of **1** (1.00 g, 2.9 mmol) in H_2O (20 ml) containing $FeSO_4 \cdot 7H_2O$ (300 mg, 1.1 mmol) and propionic acid (1.10 g, 15 mmol), conc. H_2SO_4 (11 ml) was added dropwise. To the mixture 30% H_2O_2 (720 mg, 6.4 mmol) was added dropwise with stirring in an ice-bath. The mixture was stirred at room temperature for 48 h and then diluted with H_2O. The precipitate was extracted with $CHCl_3$ (100 ml × 3). The combined extracts were evaporated, and the residue was passed through silica gel column chromatography with $CHCl_3$ to give **4b** (17 mg, 13% yield).

4c: Pale yellow needles, mp 260—261 °C ($CHCl_3$–n-C_6H_{14}). IR (KBr) ν: 1745, 1650, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, t, J=7 Hz), 1.08 (3H, t, J=8 Hz), 1.25—2.05 (4H, m), 3.26 (2H, t, J=8 Hz), 5.24 (2H, s), 5.35 (1H, d, J=17 Hz), 5.69 (1H, d, J=17 Hz), 7.67 (1H, s), 7.55—8.29 (4H, m). MS *m/z*: 390 (M^+). *Anal.* Calcd for $C_{23}H_{24}N_2O_4$: C, 70.75; H, 5.68; N, 7.18. Found: C, 70.90; H, 5.65; N, 7.12.

4d: Pale yellow needles, mp 258—259 °C ($CHCl_3$–n-C_6H_{14}). IR (KBr) ν: 1750, 1645, 1595 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, t, J=8 Hz), 1.54 (6H, d, J=7 Hz), 1.90 (2H, q, J=8 Hz), 3.9—4.1 (1H, m), 5.37 (2H, s), 5.29 (1H, d, J=17 Hz), 5.75 (1H, d, J=17 Hz), 7.63 (1H, s), 7.45—8.63 (4H, m). MS *m/z*: 390 (M^+).

4e: Pale yellow needles, mp 198—200 °C ($CHCl_3$–n-C_6H_{14}). IR (KBr) ν: 1740, 1650, 1595 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (3H, t, J=7 Hz), 1.07 (6H, d, J=7 Hz), 1.93 (2H, q, J=7 Hz), 2.12—2.41 (1H, m), 3.09 (2H, d, J=7 Hz), 5.29 (1H, d, J=16 Hz), 5.37 (2H, s), 5.54 (1H, J=16 Hz), 7.68 (1H, s), 7.55—8.29 (4H, m). MS *m/z*: 404 (M^+).

4f: Pale yellow needles, mp 206—207 °C ($CHCl_3$–n-C_6H_{14}). IR (KBr) ν: 1745, 1680, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.80—2.04 (12H, m), 3.14 (2H, t, J=7 Hz), 5.23 (2H, s), 5.26 (1H, d, J=17 Hz), 5.73 (1H, d, J=17 Hz), 7.62 (1H, s), 7.28—7.88 (2H, m), 7.96—8.26 (2H, m). MS *m/z*: 404 (M^+). *Anal.* Calcd for $C_{24}H_{24}N_2O_4$: C, 71.27; H, 5.98; N, 6.93. Found: C, 71.11; H, 5.95; N, 7.01.

4g: Pale yellow needles, mp 263—265 °C ($CHCl_3$–n-C_6H_{14}). IR (KBr) ν: 3360, 1735, 1650, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, t, J=8 Hz), 1.89 (2H, q, J=8 Hz), 4.58 (2H, s), 5.14 (2H, s), 5.26 (1H, d, J=16 Hz), 5.73 (1H, d, J=16 Hz), 7.00—7.34 (5H, m), 7.68 (1H, s), 7.55—8.23 (4H, m). MS *m/z*: 438 (M^+).

4h: Pale yellow needles, mp 260—262 °C ($CHCl_3$–n-C_6H_{14}). IR (KBr) ν: 1745, 1655, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.02 (3H, t, J=8 Hz), 4.19 (2H, q, J=8 Hz), 3.47 (2H, t, J=7 Hz), 3.80 (2H, t, J=7 Hz), 4.78 (2H, s), 5.24 (1H, d, J=17 Hz), 5.70 (1H, d, J=17 Hz), 6.98—7.40 (5H, m), 7.61 (1H, s), 7.51—8.38 (4H, m). MS *m/z*: 452 (M^+).

4i: Pale yellow needles, mp 260—262 °C ($CHCl_3$–n-C_6H_{14}). IR (KBr) ν: 1745, 1655, 1595 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, t, J=8 Hz), 1.20—2.18 (12H, m), 3.70—3.72 (1H, m), 5.39 (2H, s), 5.30 (1H, d, J=17 Hz), 5.72 (1H, d, J=17 Hz), 7.67 (1H, s), 7.50—7.85 (2H, m), 8.16—8.27 (2H, m). MS *m/z*: 430 (M^+).

5a: Colorless needles, mp 264—266 °C (EtOH). ^{1}H-NMR (DMSO-d_6) δ: 1.00 (3H, t, J=7 Hz), 1.92 (2H, q, J=7 Hz), 3.42 (2H, t, J=6 Hz), 3.99 (2H, m), 4.72 (1H, t, J=4 Hz), 5.35 (2H, s), 5.25 (1H, d, J=17 Hz), 5.65 (1H, d, J=17 Hz), 6.01 (1H, s), 7.58 (1H, s), 7.5—7.9 (2H, m), 8.1—8.20 (2H, m). MS *m/z*: 392.1352 (M^+). Calcd for $C_{22}H_{20}N_2O_5$: 392.1369.

5b: Pale yellow needles, mp 257—259 °C (EtOH). ^{1}H-NMR (DMSO-d_6) δ: 0.89 (3H, t, J=7 Hz), 1.48 (3H, d, J=6 Hz, 7-$CH(CH_3)CH_2OH$), 3.8—4.0 (3H, m), 4.90 (1H, t, J=5 Hz), 5.43 (4H, s), 6.50 (1H, s), 7.34 (1H, s), 7.6—7.9 (2H, m), 8.16 (1H, dd, J=1, 8 Hz), 8.37 (1H, d, J=7 Hz). MS *m/z*: 406.1530 (M^+). Calcd for $C_{23}H_{22}N_2O_5$: 406.1529.

5c: Pale yellow needles, mp 210—212 °C (EtOH–n-C_6H_{14}). ^{1}H-NMR (DMSO-d_6) δ: 0.89 (3H, t, J=7 Hz), 1.80—1.95 (4H, m), 3.28—3.32 (2H, m), 3.51 (2H, t, J=6 Hz), 4.68 (1H, br), 5.37 (2H, s), 5.43 (2H, s), 6.49 (1H, s), 7.33 (1H, s), 7.5—7.9 (2H, m), 8.1—8.3 (2H, m). MS *m/z*: 406.1548 (M^+). Calcd for $C_{23}H_{22}N_2O_5$: 406.1529.

5d: Colorless needles, mp 228—229 °C (EtOH). ^{1}H-NMR (DMSO-d_6) δ: 0.88 (6H, t, J=7 Hz), 1.88 (2H, q, J=7 Hz), 1.97—2.25 (2H, m), 3.90 (2H, br), 4.33 (1H, br), 4.83 (1H, br), 5.39 (1H, s), 5.44 (2H, s), 6.52 (1H, s), 7.35 (1H, s), 7.61—7.94 (2H, m), 8.18 (1H, d, J=7 Hz), 8.41 (1H, d, J=8 Hz). MS *m/z*: 420 (M^+).

5e: Colorless needles, mp 214—216 °C (EtOH). ^{1}H-NMR (DMSO-d_6) δ: 0.90 (3H, t, J=7 Hz), 1.51 (3H, d, J=7 Hz), 1.89 (2H, q, J=7 Hz), 1.92—2.20 (2H, m), 3.30—3.50 (2H, m), 3.80 (1H, br), 4.59 (1H, t, J=5 Hz), 5.39 (2H, s), 5.44 (2H, s), 6.53 (1H, s), 7.35 (1H, s), 7.63—7.94 (2H, m), 8.19 (1H, dd, J=1, 8 Hz), 8.42 (1H, d, J=8 Hz). MS *m/z*: 420.1679 (M^+). Calcd for $C_{24}H_{24}N_2O_5$: 420.1862.

5f: Colorless needles, mp 197—199 °C (EtOH–n-C_6H_{14}). ^{1}H-NMR (DMSO-d_6) δ: 0.90 (3H, t, J=7 Hz), 1.60—1.70 (4H, m), 1.88 (2H, q, J=7 Hz), 3.20 (2H, br), 3.47 (2H, q, J=6 Hz), 4.42 (1H, t, J=5 Hz), 5.26 (2H, s), 5.43 (2H, s), 6.51 (1H, s), 7.32 (1H, s), 7.63—7.91 (2H, m), 8.10—8.30 (2H, m). MS *m/z*: 420.1673 (M^+). Calcd for $C_{24}H_{24}N_2O_5$: 420.1682.

5g: Pale yellow needles, mp 211—213 °C (EtOH). ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, d, J=7 Hz), 1.04 (3H, t, J=7 Hz), 1.90 (2H, q, J=7 Hz), 2.83—3.04 (1H, m), 3.42—3.80 (4H, m), 5.20—5.83 (4H, m), 7.66 (1H, s), 7.57—7.88 (2H, m), 8.12—8.27 (2H, m). MS *m/z*: 420 (M^+).

5h: Colorless needles, mp 222—224 °C (EtOH). ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, d, J=7 Hz), 1.02 (3H, t, J=7 Hz), 1.60—1.99 (4H, m), 2.25 (1H, br), 2.94—3.39 (2H, m), 3.7—4.0 (2H, m), 5.24 (2H, s), 5.28 (1H, d, J=17 Hz), 5.68 (1H, d, J=17 Hz), 7.5—7.8 (3H, m), 8.03—8.17 (2H, m). MS *m/z*: 434 (M^+).

5i: Pale yellow needles, mp 237—239 °C (EtOH–$CHCl_3$). ^{1}H-NMR (DMSO-d_6) δ: 0.89 (3H, t, J=7 Hz), 1.28 (3H, d, J=6 Hz), 1.88 (2H, q, J=7 Hz), 3.04—3.47 (2H, m), 4.00—4.10 (1H, m), 4.85 (1H, d), 5.34 (2H, s), 5.43 (2H, s), 6.51 (1H, s), 7.34 (1H, s), 7.63—7.93 (2H, s), 8.12—8.34 (2H, m). MS *m/z*: 406 (M^+).

7-Acyloxymethylcamptothecin (6), General Procedure To a cooled solution of **2** in pyridine, an acylating agent (1.2 eq) was added dropwise. The mixture was stirred at room temperature for a few hours and then evaporated to dryness. The residue was purified through silica gel column chromatography with $CHCl_3$.

6a: Yield 78%. Pale yellow needles, mp 277—279 °C ($CHCl_3$–n-C_6H_{14}). IR (KBr) ν: 1770, 1650, 1595 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, t, J=7 Hz), 1.89 (2H, q, J=7 Hz), 2.18 (3H, s), 5.44 (2H, s), 5.26 (1H, d, J=17 Hz), 5.72 (1H, d, J=17 Hz), 5.71 (2H, s), 7.70 (1H, s), 7.58—8.28 (4H, m). MS *m/z*: 420.1369 (M^+). Calcd for $C_{23}H_{20}N_2O_6$: 420.1314. *Anal.* Calcd for $C_{23}H_{20}N_2O_6$: C, 65.71; H, 4.79; N, 6.66. Found: C, 65.36; H, 4.73; N, 6.43.

6b: Yield 86%. Pale yellow needles, mp 279—280 °C ($CHCl_3$–n-C_6H_{14}). IR (KBr) ν: 1740, 1655, 1595 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.05 (3H, t, J=7 Hz), 1.18 (3H, t, J=7 Hz), 1.91 (2H, q, J=7 Hz), 2.47 (2H, q, J=7 Hz), 5.28 (1H, d, J=17 Hz), 5.70 (1H, d, J=17 Hz), 5.44 (4H, s), 5.71 (2H, s), 7.63 (1H, s), 7.70—8.30 (4H, m). MS *m/z*: 434 (M^+). *Anal.* Calcd for $C_{24}H_{22}N_2O_6$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.37; H, 5.07; N, 6.33.

6c: Yield 71%. Pale yellow needles, mp 252—254 °C ($CHCl_3$–n-C_6H_{14}). IR (KBr) ν: 1750, 1740, 1665, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, t, J=7 Hz), 1.05 (3H, t, J=7 Hz), 1.69 (2H, sextet, J=7 Hz), 1.91 (2H, q, J=7 Hz), 2.42 (2H, t, J=7 Hz), 5.28 (1H, d, J=16 Hz), 5.72 (1H, d, J=16 Hz), 5.44 (2H, s), 5.69 (2H, s), 7.63 (1H, s), 7.58—8.25 (4H, m). MS *m/z*: 448 (M^+). *Anal.* Calcd for $C_{25}H_{24}N_2O_6$: C, 66.95; H, 5.39; N, 6.25. Found: C, 66.80; H, 5.30; N, 6.28.

6d: Yield 66%. Pale yellow needles, mp 240—242 °C ($CHCl_3$–n-C_6H_{14}). IR (KBr) ν: 1740, 1650, 1595 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (6H, d, J=7 Hz), 1.04 (3H, t, J=7 Hz), 1.91 (2H, q, J=7 Hz), 2.31 (2H, d, J=7 Hz), 3.71 (1H, m), 5.30 (1H, d, J=16 Hz), 5.69 (1H, d, J=16 Hz), 5.42 (2H, s), 5.72 (2H, s), 7.65 (1H, s), 7.57—8.27 (4H, m). MS *m/z*: 462 (M^+).

6e: Yield 49%. Pale yellow needles, mp 252—253 °C ($CHCl_3$–n-C_6H_{14}). IR (KBr) ν: 1760, 1665, 1600 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.89 (3H, t, J=7 Hz), 1.89 (2H, q, J=7 Hz), 5.40 (2H, s), 5.42 (2H, s), 5.45 (2H, s), 5.79 (2H, s), 7.25 (5H, s), 7.35 (1H, s), 7.60—8.30 (8H, m). MS *m/z*: 496 (M^+).

6f: Yield 58%. Pale yellow needles, mp 298 °C (MeOH). IR (KBr) ν: 1770, 1730, 1675, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.09 (3H, t, J=8 Hz), 1.93 (2H, q, J=8 Hz), 5.55 (4H, br s), 5.92 (2H, s), 7.47 (1H, s), 7.54—8.30 (9H, m). MS *m/z*: 482 (M^+). *Anal.* Calcd for $C_{27}H_{22}N_2O_6$: C, 69.70; H, 4.60; N, 5.81. Found: C, 69.35; H, 5.81; N, 5.62.

Reaction of 2 with Phenylacetyl Chloride A mixture of **2** (100 mg, 0.264 mmol) and phenylacetyl chloride (200 mg, 1.29 mmol) in DMF–pyridine (1 : 1, 100 ml) was stirred at 90—100 °C for 6 h. The mixture was evaporated to dryness and the residue was purified through silica gel column chromatography with $CHCl_3$ to give **6e** (74 mg, 56.6% yield) and **7** (19 mg, 19.1% yield).

7-Formylcamptothecin (7), Typical Procedure A suspension of **2** (200 mg, 0.53 mmol) in AcOH (100 ml) was heated under reflux for 5.5 h. The mixture was evaporated to dryness and the residue was purified through silica gel column chromatography with 5% MeOH–$CHCl_3$ to give **6a** (19 mg, 9% yield) and **7** (135 mg, 68% yield) as orange needles, mp 256—260 °C (aq. AcOH). IR (KBr) ν: 1750, 1690, 1655, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (H, t, J=8 Hz), 1.93 (2H, q, J=8 Hz), 5.31 (1H, d, J=16 Hz), 5.80 (1H, d, J=16 Hz), 5.63 (2H, s), 7.68 (1H, s), 7.85—7.95 (2H, m), 8.35—8.41 (1H, m), 8.77—8.83 (1H, m), 11.20 (1H, s). MS *m/z*: 376 (M^+).

7-Methoxy- and 7-Dimethoxymethylcamptothecin (8a and 9a) A solution of **2** (100 mg, 0.26 mmol) in a 1 : 1 mixture of MeOH–dioxane (40 ml) containing conc. H_2SO_4 (3 ml) was heated under reflux for 35 h. The mixture was condensed, the residue was poured into H_2O, and the precipitate was extracted with $CHCl_3$ (100 ml × 3). The combined extracts were dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified through silica gel column chromatography with 1% MeOH–$CHCl_3$.

8a: Yield 40 mg, 39%. Pale yellow needles, mp 252—257 °C (MeOH–$CHCl_3$). IR (KBr) ν: 1755, 1655, 1600 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.94 (3H, t, $J=7$ Hz), 1.88 (2H, q, $J=7$ Hz), 3.31 (3H, s), 5.20 (2H, s), 5.36 (2H, s), 5.46 (2H, s), 6.51 (1H, s), 7.39 (1H, s), 7.60—8.30 (4H, m). MS *m*/*z*: 392 (M$^+$).

9a: Yield 19 mg, 17%. Pale yellow needles, mp 222—224 °C ($CHCl_3$–n-C_6H_{14}). IR (KBr) ν: 1750, 1655, 1595 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.05 (3H, t, $J=7$ Hz), 1.90 (2H, q, $J=7$ Hz), 3.40 (3H, s), 3.41 (3H, s), 5.29 (1H, d, $J=16$ Hz), 5.77 (1H, d, $J=16$ Hz), 5.49 (2H, s), 6.25 (1H, s), 7.76 (1H, s), 7.67—8.34 (4H, m). MS *m*/*z*: 422 (M$^+$). *Anal.* Calcd for $C_{23}H_{22}N_2O_6$: C, 65.39; H, 5.25; N, 6.63. Found: C, 65.47; H, 5.19; N, 6.59.

7-Ethoxy- and 7-Diethoxymethylcamptothecin (8b and 9b) A solution of **2** (200 mg, 0.5 mmol) in a 1 : 1 mixture of EtOH and dioxane (40 ml) containing conc. H_2SO_4 (6 ml) was refluxed for 7 h. The reaction mixture was worked up as described above to give **8b**: Yield 27 mg, 21%. Pale yellow needles, mp 139—142 °C (EtOH–$CHCl_3$). IR (KBr) ν: 1740, 1655, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, t, $J=7$ Hz), 1.38 (3H, t, $J=7$ Hz), 1.83 (2H, q, $J=7$ Hz), 3.81 (2H, q, $J=7$ Hz), 5.18 (2H, s), 5.27 (1H, d, $J=17$ Hz), 5.76 (1H, d, $J=17$ Hz), 5.43 (2H, s), 7.65 (1H, s), 7.65—8.28 (4H, m). MS *m*/*z*: 406 (M$^+$). *Anal.* Calcd for $C_{23}H_{22}N_2O_5$: C, 67.96; H, 5.46; N, 6.89. Found: C, 67.69; H, 5.35; N, 6.94. **9b**: Yield 24 mg, 19%. Pale yellow needles, mp 223—224 °C ($CHCl_3$–n-C_6H_{14}). IR (KBr) ν: 1740, 1655, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, t, $J=7$ Hz), 1.26 (3H, t, $J=7$ Hz), 1.28 (3H, t, $J=7$ Hz), 1.90 (2H, q, $J=7$ Hz), 3.6—3.8 (4H, m), 5.29 (1H, d, $J=16$ Hz), 5.76 (1H, d, $J=16$ Hz), 5.50 (2H, s), 6.36 (1H, s), 7.66 (1H, s), 7.64—7.87 (2H, m), 8.17—8.39 (2H, m). MS *m*/*z*: 450 (M$^+$). *Anal.* Calcd for $C_{25}H_{26}N_2O_6$: C, 66.65; H, 5.82; N, 6.22. Found: C, 66.28; H, 5.95; N, 6.09.

7-Butoxymethylcamptothecin (8c) A suspension of **2** (100 mg, 0.26 mmol) in butanol (30 ml) containing conc. H_2SO_4 (5 ml) was heated under reflux for 2.5 h. The mixture was worked up as described above to give **4c**: Yield 48 mg, 42%. Pale yellow needles, mp 142—144 °C (EtOH–n-C_6H_{14}). IR (KBr) ν: 1745, 1660, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, $J=7$ Hz), 1.03 (3H, t, $J=6$ Hz), 1.10—1.80 (4H, m), 1.90 (2H, q, $J=7$ Hz), 3.70 (2H, t, $J=6$ Hz), 5.17 (2H, s), 5.28 (1H, d, $J=16$ Hz), 5.75 (1H, d, $J=16$ Hz), 5.42 (2H, s), 7.66 (1H, s), 7.50—8.30 (4H, m). MS *m*/*z*: 434 (M$^+$). *Anal.* Calcd for $C_{25}H_{26}N_2O_5$: C, 69.11; H, 6.03; N, 6.45. Found: C, 69.24; H, 5.98; N, 6.48.

7-Dibutoxymethylcamptothecin (9c) A solution of **2** (100 mg, 0.26 mmol) in butanol (50 ml) containing conc. H_2SO_4 (8 mg) was heated under reflux for 0.5 h. The mixture was worked up as described above to give **9c** (52 mg, 39% yield) as pale yellow needles, mp 107—111 °C ($CHCl_3$–n-C_6H_{14}). IR (KBr) ν: 1750, 1660, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, $J=7$ Hz), 1.11 (3H, t, $J=7$ Hz), 1.12 (3H, t, $J=7$ Hz), 1.14—1.79 (8H, m), 1.90 (2H, q, $J=7$ Hz), 3.47—3.67 (4H, m), 5.29 (1H, d, $J=16$ Hz), 5.77 (1H, d, $J=16$ Hz), 5.50 (2H, s), 6.36 (1H, s), 7.68 (1H, s), 7.50—7.80 (2H, m), 8.20—8.40 (2H, m). MS *m*/*z*: 506 (M$^+$).

Hydrolysis of 8b A solution of **8b** (250 mg, 0.555 mmol) in 20% HCl (40 ml) was stirred at room temperature for 18 h. The mixture was diluted with ice-H_2O and the precipitate was extracted with $CHCl_3$ (200 ml × 3). The combined extracts were evaporated and the residue was recrystallized from aqueous AcOH to give **7** (187 mg, 89.6% yield).

7-Iminomethylcamptothecins (10), General Procedure A mixture of **5** (350 mg, 0.93 mmol) and a carbonyl reagent (2.8 mmol) in a mixture of EtOH (70 ml) and pyridine (10 ml) was heated under reflux for 0.5 h. The mixture was condensed, and the residue was recrystallized.

10a: Yield 87%. Yellow prisms, mp 255—257 °C (EtOH). IR (KBr) ν: 1740, 1655, 1590 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.9 (3H, t, $J=8$ Hz), 1.92 (2H, q, $J=8$ Hz), 5.34 (2H, s), 5.43 (2H, s), 7.63 (1H, s), 7.75—8.34 (4H, m), 9.26 (1H, s), 12.54 (1H, s). MS *m*/*z*: 391 (M$^+$).

10b: Yield 71%. Yellow prisms, mp 262—265 °C (MeOH). IR (KBr) ν: 1755, 1655, 1590 cm^{-1}. MS *m*/*z*: 390 (M$^+$).

10c: Yield 74%. Yellow needles, mp 203—205 °C (EtOH). IR (KBr) ν: 1740, 1650, 1600 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.95 (3H, t, $J=7$ Hz), 1.88 (2H, q, $J=7$ Hz), 3.13 (3H, d, $J=4$ Hz), 5.35 (2H, s), 5.20 (1H, d, $J=14$ Hz), 5.60 (1H, d, $J=14$ Hz), 6.25 (1H, br s), 7.43 (1H, s), 7.50—8.80 (4H, m), 10.15 (1H, s). MS *m*/*z*: 404 (M$^+$).

10d: Yield 71%. Yellow needles, mp 205—208 °C (EtOH). IR (KBr) ν: 1735, 1655, 1600 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.97 (3H, t, $J=7$ Hz), 1.90 (2H, q, $J=7$ Hz), 5.24 (1H, d, $J=16$ Hz), 5.64 (1H, d, $J=16$ Hz), 5.48 (2H, s), 6.90 (1H, br s), 7.00—8.90 (9H, m), 7.48 (1H, s), 11.24 (1H, br s). MS *m*/*z*: 466 (M$^+$).

10e: Yield 83%. Colorless needles, mp 250 °C (EtOH). IR (KBr) ν: 1743, 1655, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.05 (3H, t, $J=7$ Hz), 1.89 (2H, q, $J=7$ Hz), 2.44 (3H, s), 2.72 (4H, t, $J=8$ Hz), 3.53 (4H, t, $J=8$ Hz), 5.41 (2H, s), 5.31 (1H, d, $J=16$ Hz), 5.73 (1H, d, $J=16$ Hz), 7.62 (1H, s), 7.40—8.30 (5H, m). MS *m*/*z*: 473 (M$^+$).

10f: Yield 91%. Pale yellow needles, mp 283 °C (EtOH). IR (KBr) ν: 1740, 1690, 1655, 1585 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.90 (3H, t, $J=7$ Hz), 1.88 (2H, q, $J=7$ Hz), 5.43 (2H, s), 5.35 (2H, s), 6.65 (2H, br), 7.35 (1H, s), 7.80—8.30 (6H, m), 8.86 (1H, s), 10.85 (1H, s).

Camptothecin 7-Carboxylic Acid (11) To a solution of **2** (1.00 g, 2.6 mmol) in conc. H_2SO_4 (10 ml), sodium dichromate (1.00 g, 3.82 mmol) was added with stirring in an ice-salt bath. The mixture was stirred at room temperature for 2 h and then poured into H_2O; the precipitate was collected by suction, and the solid was purified by recrystallization to give **11** (815 mg, 79% yield) as yellow needles, mp 280 °C (pyridine). IR (KBr) ν: 1760, 1650, 1595 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.91 (3H, t, $J=7$ Hz), 1.90 (2H, q, $J=7$ Hz), 5.31 (2H, s), 5.41 (2H, s), 6.50 (1H, br s), 7.30 (1H, s), 7.65—8.84 (4H, m). MS *m*/*z*: 392.0995 (M$^+$). Calcd for $C_{21}H_{16}N_2O_6$: 392.1002.

Esters (12), General Procedure To a solution of **11** (200 mg, 0.51 mmol) in DMF (30 ml), K_2CO_3 (200 mg, 1.1 mmol) and an alkylating reagent (5 eq, methyl *p*-toluenesulfonate, ethyl bromide, benzyl chloride) were added. The mixture was stirred at room temperature for 2 h and then passed through a celite pad by suction. The filtrate was evaporated to dryness, and the residue was purified through silica gel column chromatography with $CHCl_3$.

12a: Yield 87%. Yellow needles, mp 245—246 °C ($CHCl_3$–n-C_6H_{14}). ^{1}H-NMR ($CDCl_3$) δ: 1.05 (3H, t, $J=8$ Hz), 1.91 (2H, q, $J=8$ Hz), 4.17 (3H, s), 5.49 (2H, s), 5.32 (1H, d, $J=17$ Hz), 5.74 (1H, d, $J=17$ Hz), 7.66 (1H, s), 7.74—7.88 (2H, m), 8.27—8.89 (2H, m). MS *m*/*z*: 406 (M$^+$). *Anal.* Calcd for $C_{22}H_{18}N_2O_6$: C, 65.02; H, 4.46; N, 6.89. Found: C, 64.95; H, 4.51; N, 6.84.

12b: Yield 89%. Yellow needles, mp 239—241 °C ($CHCl_3$–n-C_6H_{14}). ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, t, $J=7$ Hz), 1.56 (3H, t, $J=7$ Hz), 1.90 (2H, q, $J=7$ Hz), 4.63 (2H, q, $J=7$ Hz), 5.47 (2H, s), 5.32 (1H, d, $J=17$ Hz), 5.72 (1H, d, $J=17$ Hz), 7.61 (1H, s), 7.70—7.86 (2H, m), 8.27—8.85 (2H, m). MS *m*/*z*: 420 (M$^+$). *Anal.* Calcd for $C_{23}H_{20}N_2O_6$: C, 65.71; H, 4.79; N, 6.66. Found: C, 65.84; H, 4.80; N, 6.63.

12c: Yield 79%. Yellow needles, mp 208—210 °C ($CHCl_3$–n-C_6H_{14}). ^{1}H-NMR ($CDCl_3$) δ: 1.04 (6H, t, $J=7$ Hz), 1.45—1.98 (6H, m), 4.57 (2H, q, $J=7$ Hz), 5.46 (2H, s), 5.31 (1H, d, $J=17$ Hz), 5.73 (1H, d, $J=17$ Hz), 7.64 (1H, s), 7.69—7.76 (2H, m), 8.24—8.84 (2H, m). *Anal.* Calcd for $C_{25}H_{24}N_2O_6$: C, 66.95; H, 5.49; N, 6.24. Found: C, 66.90; H, 5.49; N, 6.24.

12d: Yield 91%. Yellow needles, mp 237—240 °C ($CHCl_3$–n-C_6H_{14}). ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, t, $J=7$ Hz), 1.88 (2H, q, $J=7$ Hz), 5.40 (2H, s), 5.30 (1H, d, $J=17$ Hz), 5.72 (1H, d, $J=17$ Hz), 5.59 (2H, s), 7.39—7.83 (7H, m), 7.61 (1H, s), 8.21—8.81 (2H, m). *Anal.* Calcd for $C_{28}H_{22}N_2O_6$: C, 69.70; H, 4.60; N, 5.81. Found: C, 69.40; H, 4.51; N, 5.56.

Preparation of 12a with Sulfuric Acid in MeOH A solution of **11** (100 mg, 0.255 mmol) in MeOH (40 ml) containing conc. H_2SO_4 (0.5 ml) was heated under reflux for 36 h. The mixture was diluted with ice-water (100 ml) and the solution was extracted with $CHCl_3$ (100 ml × 2). The combined extracts were dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue was purified through silica gel column chromatography with $CHCl_3$ to give **12a** (23 mg, 22.2% yield).

Amides (13), General Procedure To a solution of **11** (500 mg, 1.3 mmol) in CH_2Cl_2 (100 ml) containing Et_3N (0.8 ml), $ClCO_2Et$ (0.8 ml, 8.8 mmol) was added dropwise with stirring in an ice-salt bath. The mixture was stirred for 0.5 h and then ammonia or amine (5 eq) was added. The mixture was stirred at room temperature for 3 h and evaporated to dryness. The residue was passed through silica gel column chromatography with 2% MeOH–$CHCl_3$.

13a: Yield 90%. Yellow needles, mp 293—295 °C (pyridine–MeOH). IR (KBr) ν: 1740, 1675, 1660, 1590 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.9 (3H, t, $J=7$ Hz), 1.88 (2H, q, $J=7$ Hz), 5.32 (2H, s), 5.48 (2H, s), 6.52 (1H, s), 7.37 (1H, s), 7.74—8.34 (6H, m). MS *m*/*z*: 391 (M$^+$).

13b: Yield 66%. Yellow needles, mp 263—266 °C (aq. MeOH). IR (KBr) ν: 1760, 1640, 1580 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.89 (3H, t, $J=7$ Hz), 1.25 (3H, t, $J=7$ Hz), 1.87 (2H, q, $J=7$ Hz), 3.30 (2H, m), 5.28 (2H, s), 5.43 (2H, s), 6.52 (1H, s), 7.37 (1H, s), 7.83—8.26 (4H, m), 8.96 (1H, m). MS m/z: 419 (M^+).

13c: Yield 78%. Yellow needles, mp 267—269 °C (aq. MeOH). IR (KBr) ν: 1740, 1655, 1590 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.89 (3H, t, $J=7$ Hz), 1.88 (2H, t, $J=7$ Hz), 4.62 (2H, d, $J=6$ Hz), 5.28 (2H, s), 5.43 (2H, s), 6.52 (1H, s), 7.30—7.50 (6H, m), 7.75—8.28 (4H, m), 9.42 (1H, m). MS m/z: 481 (M^+).

13d: Yield 90%. Yellow needles, mp 283—285 °C (aq. MeOH). ^{1}H-NMR (DMSO-d_6) δ: 0.89 (3H, t, $J=7$ Hz), 1.88 (2H, q, $J=7$ Hz), 2.80 (3H, s), 3.21 (3H, s), 5.01 (1H, d, $J=17$ Hz), 5.40 (1H, d, $J=17$ Hz), 5.43 (2H, s), 6.53 (1H, s), 7.37 (1H, s), 7.75—8.28 (4H, m). MS m/z: 419 (M^+).

13e: To a suspension of **11** (100 mg, 0.225 mmol) in dioxane (50 ml), DCC (100 mg, 0.485 mmol) was added. The mixture was stirred at room temperature for 30 min, to the mixture cyclohexylamine (2 ml) was added dropwise. The mixture was stirred at room temperature for 6 h and worked-up as described above to give **13e** (29% yield) as yellow needles, mp 252—254 °C (aq. EtOH). IR (KBr) ν: 1755, 1660, 1595 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.89 (3H, t, $J=7$ Hz), 1.3—1.9 (12H, m), 3.90 (1H, br), 5.24 (2H, s), 5.42 (2H, s), 6.49 (1H, s), 7.37 (1H, s), 7.73—8.24 (4H, m), 8.78 (1H, d, $J=8.5$ Hz). MS m/z: 473 (M^+).

Antitumor Activity L1210 leukemia cells (10^5) were implanted intraperitoneally (i.p.) in 7 week old BDF$_1$ female mice on day 0, and 10 mice were used at each dose. Samples were suspended in saline and the suspension was administered i.p. days 1 to 5. The control mice were injected with saline and cured mice were calculated on day 40.

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