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Semisynthesis of DB-67 and Other Silatecans from Camptothecin by Thiol-Promoted Addition of Silyl Radicals

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Dedicated to Professor Lutz F. Tietze on the occasion of his 60th birthday.

Abstract—Thiol- or acid-promoted additions of silyl radicals to camptothecin are reported. At 105 °C, mixtures of 7-silyl (favored) and 12-silyl camptothecins are formed alongside substantial amounts of recovered camptothecin. At 160 °C, 12-silyl isomers are formed preferentially, but the total mass balance is substantially reduced. The silyl radical addition is featured in short semi-syntheses of DB-67 (7-*tert*-butyldimethylsilyl-10-hydroxy camptothecin) from both camptothecin and 10-hydroxycamptothecin.

Introduction

Analogues of the natural product camptothecin **1a** are important for treatment of solid tumors. Water soluble analogues such as topotecan **1b** and irinotecan **1c** (Fig. 1) are already approved in several countries for clinical use.[1] Lipophilic analogues of camptothecin have distinct properties, and several of these are in various stages of development.[2] 7-Silylcamptothecins **2**, or silatecans, are an important class of lipophilic camptothecin analogues,[3] and 7-*tert*-butyldimethylsilyl-10-hydroxy camptothecin **2a** (DB-67) is currently in late stages of preclinical development.[4] DB-67 shows a number of attractive features including high activity against a broad spectrum of solid tumors, low binding to blood proteins, resistance to lactone opening and high lipophilicity, among others.

DB-67 and related silatecans have been prepared in enantiopure form by total synthesis using the cascade radical annulation route.[5] This synthesis is highly flexible and allows the preparation of a diverse array of silatecan analogues by both traditional and parallel routes.[5a] However, the total synthesis of silatecans like DB-67 takes about 14 steps and proceeds in about 2% overall yield. DB-67 has already been prepared on about 60 g scale by total synthesis, but a shorter route would be advantageous. In this paper, we describe a semisynthesis of silatecans from camptothecins by addition of silyl radicals. The usefulness of this new silyl radical addition reaction is highlighted by three-step semi-syntheses of DB-67 from both camptothecin and 10-hydroxy camptothecin.

Silyl radical additions to pyridines and quinolines do not appear to be known, but additions to alkenes are common,[6,7] and additions to benzene rings[8] and fullerenes[9] are also known. Sawada et al.[10] have made 7-alkyl-substituted camptothecins from camptothecin itself by addition of alkyl radicals according to the standard Minisci reaction,[11] so we were encouraged that silyl radicals might add selectively to the 7-position of camptothecin. But Minisci reaction conditions are not applicable to the generation of silyl radicals since the needed precursors (for example, formyl silanes) are difficult to make and unstable.[12] In addition, strong acids are required in the Minisci reaction, and this limits the substituents that can be present on the camptothecin ring.

Results and Discussion

Thermal or photochemical decomposition of a peroxide in the presence of a silane is a common method to

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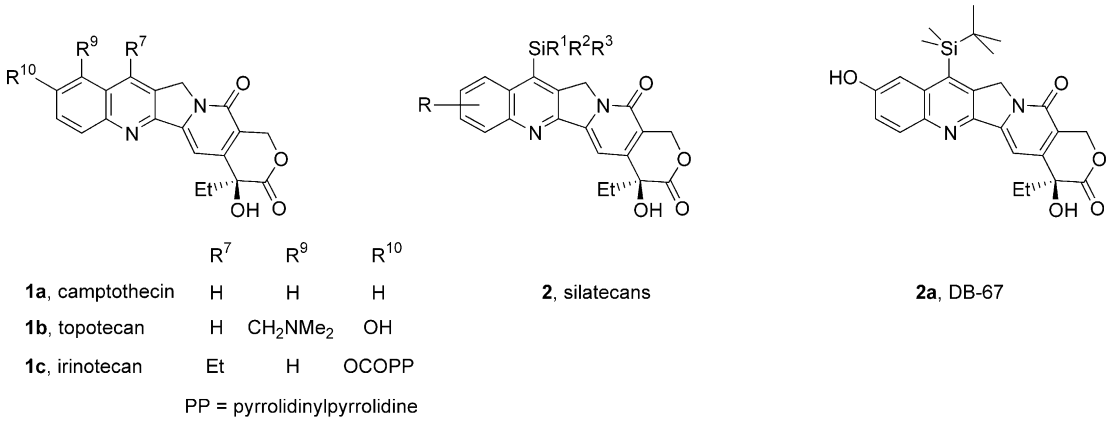


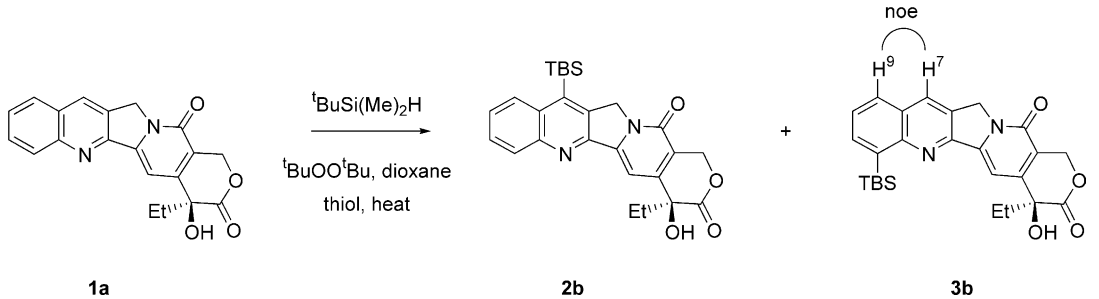
Figure 1. Structures of camptothecin and selected analogues.

generate silyl radicals,[6] although it is used much more often for esr and kinetic studies than for preparative transformations. Initial experiments with this method were not very successful. For example, irradiation of a mixture of camptothecin **1a**, *tert*-butyldimethylsilane and di-*tert*-butylperoxide in dichloromethane or trifluoroacetic acid produced only a faint TLC spot with the R_f corresponding to authentic 7-*tert*-butyldimethylsilylcamptothecin. UV detection is very sensitive for camptothecin analogues, so these qualitative experiments showed that only traces of the desired product were formed at most.

In exploring various reaction conditions and additives, we discovered that certain thiols had a very beneficial effect.[13] The results of several key experiments are summarized in eq 1 and Table 1. Heating of camptothecin **1a**, *tert*-butyldimethylsilane (10 equiv), di-*tert*-butylperoxide (1.7 equiv) and *tert*-butane thiol (2 equiv) in dioxane at reflux for 36 h (Table 1, entry 1) followed by chromatographic separation provided (in order of elution) 7-*tert*-butyldimethylsilylcamptothecin **2b** (20%), 12-*tert*-butyldimethylsilylcamptothecin **3b** (10%) and recovered camptothecin **1a** (57%). 7-*tert*-Butyldimethylsilylcamptothecin **2b** was identical to an authentic sample prepared by total synthesis.[5d] 12-*tert*-Butyldimethylsilylcamptothecin was identified by ^{1}H NMR experiments. Two doublets and a triplet in the aromatic region show that the three A-ring protons are all adjacent. This leaves two possibilities, 9-silyl- and 12-silyl-substitution, and noe studies supported the latter assignment (a strong noe was observed between H^7 and H^9).

Three other thiols were also tried under comparable conditions and the results are shown in Table 1, entries 2–4. *tert*-Dodecane thiol was inferior to *tert*-butane thiol while propane dithiol did not work at all. Triisopropylsilanethiol was roughly comparable to *tert*-butane thiol. Solvent choices are limited by the solubility of camptothecin, and reactions in DMSO and *tert*-butanol were inferior to dioxane. Attempts to push the reaction to further conversion by heating for longer times or addition of more thiol or peroxide were not very successful. Heating the reaction to 160 °C provided only the 12-silyl isomer along with a greatly reduced amount of recovered camptothecin (entry 5).

Thiols are known to facilitate hydrogen abstraction from silanes.[13] While the complete mechanism of this thiol addition is unclear, we speculate that decomposition of *tert*-butyl peroxide to the *tert*-butyl peroxy radical is followed by competitive hydrogen abstraction from the silane, the thiol and the solvent. Since it is present in large excess, the solvent probably reacts most often. The resulting dioxanyl radical probably abstracts a hydrogen atom from the thiol, which in turn abstracts a hydrogen atom from the silane in a relay process. Addition of the silyl radical then occurs competitively at C7 and C12, followed by oxidative rearomatization. The mechansim of the oxidative rearomatization is not known,[14] nor is it known whether the silyl radical addition is reversible,[6] so it is not clear why the 12-silyl product dominates at higher temperature. The interpretation of the temperature trend is further complicated by the known thermal instability of camptothecins



Eq 1.

Table 1. Thiol promoted additions of $^{t}BuSi(Me_2)H$ to camptothecin

Entry	Thiol	Temp °C	Yield **2b**	Yield **3b**	Recovered **1a**
1	$^{t}BuSH$	105	22%	10%	57%
2	$^{t}C_{12}H_{25}SH$	105	5%	4%	70%
3	HSC_3H_6SH	105	—[a]	—[a]	100%
4	$(ipr)_3SiSH$	105	23%	11%	60%
5	$^{t}BuSH$	160	—[a]	22%	20%

[a]Little or no product detected by TLC analysis.

at high temperature,[15] which may account for the lower total yields at 160 °C.

The generality of these reaction conditions was shown by heating a series of silanes with triisopropylsilanethiol at the reflux point of dioxane or with *tert*-butyl thiol in a sealed tube at 105°C and 160°C. The initial observations with *tert*-butyldimethylsilane proved to be quite general. At the lower temperature (Table 2, entries 1–6), the 7-silylisomer **2** was isolated in 20–31% yield alongside lesser amounts of the 12-silyl isomer **3** (7–19%). Most of the balance of the material (50–67%) was recovered camptothecin, which was reused in subsequent experiments. At the higher temperature (Table 2, entries 7–10), little or no 7-silylisomer **2** was observed and the 12-silyl isomer **3** was isolated in 26–37% yield with only 10–19% recovered camptothecin.

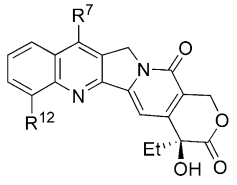
7-Silyl derivatives **2c**,**e**,**f**,**h** are known compounds and were identical to authentic samples,[16,17] while derivatives **2d** and **2g** are new and were fully characterized. All of the 12-silyl derivatives are new compounds.

Camptothecin is readily available in large quantities and with the above procedure it can now be converted into 7-*tert*-butyldimethylsilyl camptothecin **2b** in about 20% yield with recovery of very substantial amounts (57%) of unreacted camptothecin. We therefore developed a method to convert 7-*tert*-butyldimethylsilyl camptothecin **2b** to DB-67 **2a** following the method of Sawada[10b,18] (for 7-ethyl camptothecin), as shown in Figure 2. Oxidation of **2** with hydrogen peroxide in acetic acid provided *N*-oxide **4** in 81% yield. Photolysis of **4** in dioxane with sulfuric acid provided DB-67 **2a** in 58% yield, identical to a sample of DB-67 prepared by total synthesis. This semi-synthesis occurs in about 10% overall yield for the three steps, not including the recovered camptothecin from the first step.

DB-67 **2a** can also be made from 10-hydroxycamptothecin (**5**) as shown in Figure 3. 10-Hydroxycamptothecin (**5**) was prepared by the literature method[19] or purchased from a commercial source. Acetylation of **5** with acetic anhydride in pyridine at room temperature gave the diacetate **6** in 84% yield. Silylation of **6** with *tert*-butyldimethylsilane in dichloroethane and trifluoroacetic acid as co-solvent/catalyst in the presence of *tert*-butyl peroxide as initiator at reflux for 48 h afforded 7-*tert*-butyldimethylsilylcamptothecin diacetate **7** in about 5% yield. When the solvent was switched to dioxane, and either triisopropylsilanethiol or *tert*-butanethiol was added, the yield improved substantially. HPLC analysis of reaction mixture after 30 h reflux showed the formation of **7** in 22% yield along with 12-silyl isomer **8** (14%) and 7,12-bis-silyl compound **9** (9%), along with diacetate **6** (approximately 10%). Prolonged heating of the reaction mixture led to only increase of **9** at the expense of **7**.

In a preparative experiment starting from 51 g of diacetate **6**, 8.3 g of pure **7** (13%) was isolated after chromatography and crystallization. Representative samples of **9** and **8** were isolated and identified by ^1H NMR spectra and elemental analyses. Deacylation of **7** with aqueous HCl/ethanol then provided DB-67 **2a** in 83% yield. Deacylation was also accomplished by sodium methoxide/methanol to yield **2a** in 71% yield. Treatment of **8** and **9** with sodium methoxide/methanol afforded **3a** and **10** respectively in moderate yield. This three-step route provides DB-67 in about 9% overall yield, but because no photolysis is required, the synthetic route may be more amenable to larger scale application.

Table 2. Addition of silyl radicals to camptothecin at lower (105 °C) and higher (160 °C) temperatures



Entry	Silanyl group on silane ($R^1R^2R^3SiH$)	Temp °C	7-Silyl Isomer (R^7 = silyl, R^{12} = H)		12-Silyl Isomer (R^7 = H, R^{12} = silyl)		Recovered **1**
1	Et_3Si	105	**2c**	30%	**3c**	11%	57%
2	$iprSi(Me)_2$	105	**2d**	31%	**3d**	8%	57%
3	$(pr)_3Si$	105	**2e**	22%	**3e**	15%	63%
4	$PhSi(Me)_2$	105	**2f**	23%	**3f**	7%	65%
5	$c\text{-}C_6H_{11}Si(Me)_2$	105	**2g**	22%	**3g**	19%	50%
6	Et_2SiMe	105	**2h**	20%	**3h**	8%	67%
7	Et_3Si	160	**2c**	—[a]	**3c**	37%	19%
8	$IprSi(Me)_2$	160	**2d**	—[a]	**3d**	30%	19%
9	$c\text{-}C_6H_{11}Si(Me)_2$	160	**2g**	—[a]	**3g**	26%	10%
10	Et_2SiMe	160	**2h**	—[a]	**3h**	26%	10%

[a]Little or no product detected by TLC.

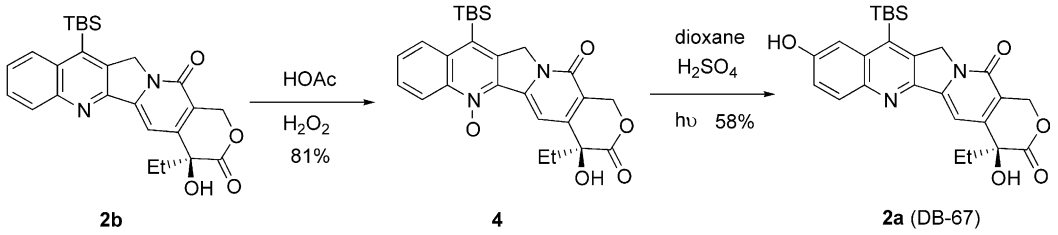


Figure 2. Semisynthesis of DB-67 from camptothecin.

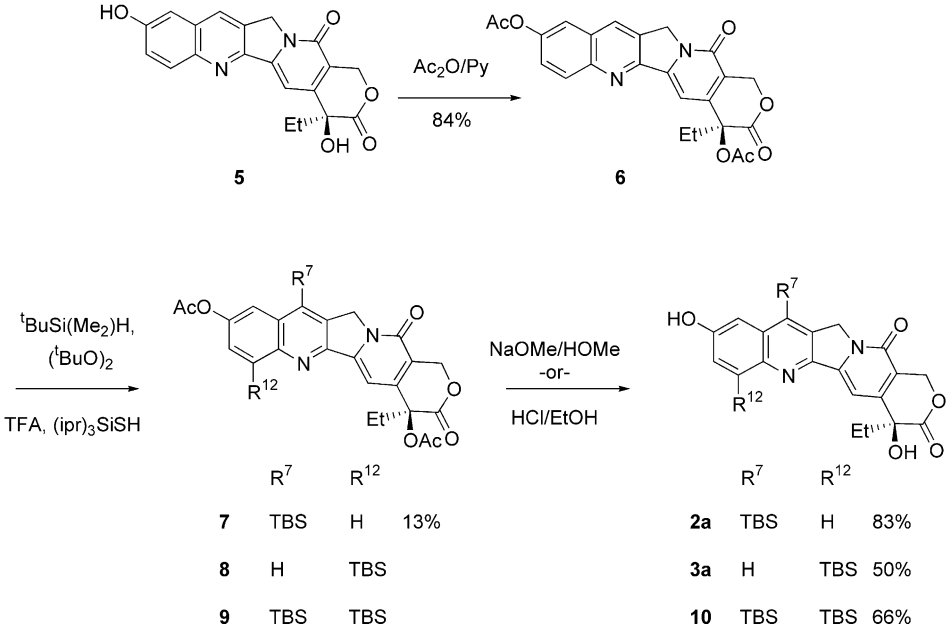


Figure 3. Semisynthesis of DB-67 from 10-hydroxycamptothecin.

Conclusions

The addition of silyl radicals to camptothecin occurs predominately at C7 or C12 depending on temperature and can be promoted by additions of either thiols or organic acids. Despite the relatively low conversions, this reaction serves as the key step in semi-syntheses of silatecans like DB-67 that are both significantly shorter and higher yielding than total synthesis by the cascade radical annulation approach. The increased accessibility of these silatecans should facilitate their development as anti-tumor agents.

Experimental

General procedure A: synthesis of 7-silyl and 12-silyl camptothecins 2 at 105 °C. To a suspension of camptothecin **1a** (50 mg, 0.14 mmol) in *p*-dioxane (15 mL) was added the corresponding silane (0.8 mL), triisopropylsilanethiol (50 μL, 0.23 mmol) and *t*-butyl peroxide (50 μL, 0.27 mmol). This suspension was then refluxed under argon for 36 h, cooled and evaporated to dryness under reduced pressure. The brown residue was then suspended in CH_2Cl_2 and applied to a silica gel column. Flash chromatography (CH_2Cl_2 followed by 5% acetone in CH_2Cl_2) yielded, in the order of elution, the 7-silyl camptothecin **2**, the 12-silyl camptothecin **3**, and unreacted camptothecin.

(20*S*)-7-*t*-Butyldimethylsilyl camptothecin (2b). Using the general procedure A, 15 mg of the title compound was prepared from camptothecin (50 mg, 0.14 mmol) as yellow solid in 23% yield. The reaction also gave 12-*t*-butyldimethylsilylcamptothecin **3b** (7 mg, 11% yield) and recovered camptothecin (30 mg, 60%). $[\alpha]_D^{20} = +47.2$ (c 2.87, CH_2Cl_2); IR 3357 (br), 2930, 2857, 1750, 1659, 1595, 1465, 1378, 1265, 1226, 1157, 1047, 832, 728; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.714 (s, 6H), 1.00 (s, 9H), 1.05 (t, $J = 7.5$, Hz, 3H), 1.91 (m, 2H), 3.76 (s, 1H), 5.37 (d, $J = 16.2$ Hz, 1H), 5.33 (s, 2H), 5.77 (d, $J = 16.2$, 1H), 7.63 (td, $J = 9.0$, 1.5 Hz, 1H), 7.68 (s, 1H), 7.79 (td, $J = 7.5$, 1.5 Hz, 1H), 8.23 (d, $J = 7.5$ Hz, 1H), 8.24 (d, $J = 9.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −0.6, 7.8, 19.2, 27.1, 31.6, 52.4, 66.3, 72.8, 97.7, 127.0, 129.4, 129.6, 130.8, 132.7, 136.0, 143.0, 146.4, 148.0, 150.2, 157.4, 173.9; HRMS *m*/*z* calcd for $C_{26}H_{30}N_2O_4Si$ 462.1975, found 462.1970.

(20*S*)-7-Triethylsilyl camptothecin (2c). Using the general procedure A, 8.8 mg of the title compound was

prepared from camptothecin (22 mg, 0.06 mmol) in 30% yield as yellow solid. The reaction also gave 12-triethylsilylcamptothecin **3c** (3.1 mg, 11%) and recovered camptothecin (12.5 mg, 57%). $[\alpha]_D^{20} = +38.1$ (c 0.26, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.99 (t, $J = 7.9$ Hz, 9H), 1.05 (t, $J = 7.3$ Hz, 3H), 1.13 (q, $J = 7.9$ Hz, 6H), 1.93 (m, 2H), 3.76 (s, 1H), 5.32 (d, $J = 16.2$ Hz, 1H), 5.33 (s, 2H), 5.77 (d, $J = 16.2$, 1H), 7.65 (td, $J = 7.5$, 1.2 Hz, 1H), 7.68 (s, 1H), 7.80 (td, $J = 7.4$, 0.8 Hz, 1H), 8.24 (d, $J = 6.6$ Hz, 1H), 8.26 (d, $J = 7.2$ Hz, 1H); HRMS m/z calcd for $C_{26}H_{30}N_2O_4Si$ 462.1975, found 462.1985.

(20*S*)-7-Isopropyldimethylsilyl camptothecin (2d). Using the general procedure A, 22 mg of the title compound was prepared in 31% yield as yellow solid from camptothecin (50 mg, 0.14 mmol). The reaction also gave 12-isopropyldimethylsilyl camptothecin 3d (6 mg, 8%) and recovered camptothecin (33.2 mg, 57%). $[\alpha]_D^{20} = +42.1$ (c 1.01, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.65 (s, 6H), 1.00 (d, $J = 7.4$ Hz, 3H), 1.02 (d, $J = 7.4$ Hz, 3H), 1.05 (t, $J = 7.3$, Hz, 3H), 1.49 (hep, 7.4 Hz, 1H), 1.91 (m, 2H), 5.32 (d, $J = 16.2$ Hz, 1H), 5.33 (s, 2H), 5.76 (d, $J = 16.2$, 1H), 7.65 (ddd, $J = 8.4$, 6.7, 1.1 Hz, 1H), 7.74 (s, 1H), 7.81 (ddd, $J = 8.4$, 7.1, 1.1 Hz, 1H), 8.23 (d, $J = 8.4$ Hz, 1H), 8.24 (d, $J = 8.4$ Hz, 1H); HRMS m/z calcd for $C_{25}H_{28}N_2O_4Si$ 448.1818, found 448.1815.

(20*S*)-7-Tripropylsilyl camptothecin (2e). Using the general procedure A, 16.6 mg of the title compound was prepared in 22% yield from camptothecin (50 mg, 0.14 mmol) as yellow solid. The reaction also gave 12-tripropylsilyl camptothecin **3e** (11.2 mg, 15%) recovered camptothecin (63%). $[\alpha]_D^{20} = +39.4$ (c 0.49, CH_2Cl_2); IR 3325 (br), 2956, 2927, 2869, 1750, 1659, 1596,1556, 1224, 1157, 1056, 762, 728; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.98 (t, $J = 7.2$ Hz, 9H), 1.03 (t, $J = 7.4$, Hz, 3H), 1.15 (m, 6H), 1.35 (m, 6H), 1.91 (m, 2H), 3.75 (s, 1H), 5.32 (d, $J = 16.3$ Hz, 1H), 5.33 (s, 2H), 5.77 (d, $J = 16.3$, 1H), 7.65 (td, $J = 8.2$, 1.3 Hz, 1H), 7.68 (s, 1H), 7.80 (td, $J = 8.0$, 0.9 Hz, 1H), 8.24 (d, $J = 6.7$ Hz, 1H), 8.27 (d, $J = 7.4$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 7.9, 16.7, 17.8, 18.4, 31.7, 52.0, 66.5, 72.9, 97.8, 18.2, 27.4, 128.0, 129.8, 131.2, 132.6, 135.7, 143.4, 146.6, 147.9, 150.2, 150.9, 157.6, 174.1; HRMS m/z calcd for $C_{29}H_{36}N_2O_4Si$ 504.2444, found 504.2467.

(20*S*)-7-Phenyldimethylsilyl camptothecin (2f). Using the general procedure A, 16 mg of the title compound was prepared in 23% yield from camptothecin (50 mg, 0.14 mmol) as yellow solid. The reaction also gave 12-phenyldimethylsilyl camptothecin **3f** (4.6 mg, 7%) and recovered camptothecin (65%). $[\alpha]_D^{20} = +44.9$ (c 0.74, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (s, 6H), 1.03 (t, $J = 7.5$, Hz, 3H), 1.88 (m, 2H), 4.95 (s, 2H), 5.27 (d, $J = 16.4$ Hz, 1H), 5.71 (d, $J = 16.4$, 1H), 7.37–7.59 (m, 6H), 7.74 (s, 1H), 7.77 (t, $J = 7.2$, 1H), 8.14 (d, $J = 8.5$ Hz, 1H), 8.29 (d, $J = 8.4$ Hz, 1H); HRMS m/z calcd for $C_{28}H_{26}N_2O_4Si$ 482.1662, found 482.1663.

(20*S*)-7-Cyclohexyldimethylsilyl camptothecin (2g). Using the general procedure A, 16.3 mg of title compound was prepared in 22% yield from camptothecin (50 mg, 0.14 mmol) as yellow solid. The reaction also gave 12-cyclohexyldimethylsilyl camptothecin 3g (19.4 mg, 19%) and recovered camptothecin (50%). $[\alpha]_D^{20} = +27.9$ (c 0.48, CH_2Cl_2); IR 3313 (br), 2919, 2845, 1749, 1658, 1596, 1556, 1446, 1256, 1225, 1157, 1047, 910, 728; ^1H NMR (500 MHz, $CDCl_3$) δ 0.64 (s, 6H), 1.05 (t, $J = 7.4$ Hz, 3H), 1.21 (m, 6H), 1.66 (m, 5H), 1.88 (m, 2H), 3.79 (s, 2H), 5.31 (s, 2H), 5.31 (d, $J = 16.3$ Hz, 1H), 5.76 (d, $J = 16.3$, 1H), 7.64 (td, $J = 7.3$, 0.9 Hz, 1H), 7.67 (s, 1H), 7.79 (t, $J = 7.2$, 1H), 8.21 (d, $J = 8.0$ Hz, 1H), 8.23 (d, $J = 7.4$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −1.4, 7.9, 26.6, 26.7, 27.5, 27.8, 31.7, 52.2, 66.5, 72.9, 97.8, 118.3, 127.3, 128.5, 129.8, 131.1, 132.4, 135.6, 143.6, 146.6, 148.0, 150.2, 150.8, 157.6, 174.1; HRMS m/z calcd for $C_{28}H_{32}N_2O_4Si$ 488.2131, found 488.2155.

(20*S*)-7-Diethylmethylsilyl camptothecin (2h). Using the general procedure A, 13.1 mg of the title compound was prepared in 20% yield from camptothecin (50 mg, 0.14 mmol) as yellow solid. The reaction also gave 12-diethylmethylsilyl camptothecin **3h** (5.2 mg, 8%) and recovered camptothecin (67%). $[\alpha]_D^{20} = +50.0$ (c 0.23, CH_2Cl_2); IR 3319 (br), 2959, 2876, 1748, 1658, 1595, 1557, 1225, 1157, 1047, 727; ^1H NMR (500 MHz, $CDCl_3$) δ 0.67 (s, 3H), 0.95–1.19 (m, 13H), 1.90 (m, 2H), 3.77 (s, 1H), 5.31 (d, $J = 16.2$ Hz, 1H), 5.33 (s, 2H), 5.76 (d, $J = 16.2$, 1H), 7.64 (td, $J = 8.2$, 1.0 Hz, 1H), 7.68 (s, 1H), 7.79 (td, $J = 8.2$, 0.9 Hz, 1H), 8.23 (d, $J = 8.7$ Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ −2.7, 7.5, 7.7, 7.9, 31.7, 52.1, 66.5, 72.9, 97.8, 118.3, 127.4, 128.1, 129.8, 131.1, 132.4, 135.7, 143.0, 146.6, 148.0, 150.2, 150.9, 157.6, 174.1. HRMS m/z calcd for $C_{25}H_{28}N_2O_4Si$ 448.1818, found 448.1815.

General procedure B: synthesis of 12-silyl camptothecins at 160 °C. To a suspension of camptothecin **1a** (20 mg, 0.057 mmol) in dioxane (2 mL) in a pressure tube was added the corresponding silane (0.5 mL) followed by 20 μL of *tert*-butylperoxide (20 μL, 0.09 mmol) and triisopropylsilanethiol or *t*-BuSH (0.11 mmol). The pressure tube was then sealed and heated to 160 °C for 16 h. After evaporation of the volatile components, the residue was purified by flash chromatography (5% acetone in dichloromethane) on silica gel column to give the 12-silyl camptothecin **3** and recovered camptothecin.

(20*S*)-12-*t*-Butyldimethylsilyl camptothecin (3b). Using the general procedure B, 5.8 mg of the title compound was prepared from camptothecin (20 mg, 0.057 mmol) in 22% yield as pale yellow solid, in addition to recovered camptothecin (20%). $[\alpha]_D^{20} = +75.0$ (c 0.04 CH_2Cl_2); IR 3380 (br), 2927, 2854, 1747, 1658, 1602, 1557, 1487, 1401, 1247, 1223, 1157, 1046, 840, 769, 732; ^1H NMR (500 MHz, $CDCl_3$) δ 0.56 (s, 6H), 0.98 (s, 9H), 1.06 (t, $J = 7.4$ Hz, 3H), 1.94 (m, 2H), 3.76 (s, 1H), 5.31 (s, 2H), 5.32 (d, $J = 16.1$ Hz, 1H). 5.77 (d, $J = 16.1$ Hz, 1H), 7.54 (s, 1H), 7.64 (t, $J = 7.4$ Hz, 1H), 7.93 (d, $J = 7.4$ Hz, 1H), 8.00 (d, $J = 7.4$ Hz, 1H), 8.37 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −3.3, 7.8, 17.7, 27.7, 31.5, 50.3, 66.5, 72.8, 97.7, 118.3, 127.4, 127.9, 129.3, 131.3, 138.6, 141.1, 147.1, 150.3, 151.1, 153.3, 157.8, 174.1; HRMS m/z calcd for $C_{26}H_{30}N_2O_4Si$ 462.1975, found 462.1972.

(20*S*)-12-Triethylsilyl camptothecin (3c). Using the general procedure B, 9.8 mg of the title compound was prepared from camptothecin (20 mg, 0.057 mmol) in 37% yield as pale yellow solid in addition to recovered camptothecin (19%). $[\alpha]_D^{20} = +16.1$ (c 0.33, CH_2Cl_2); IR 2926, 2874, 1744, 1659, 1603, 1557, 1463, 1224, 1157, 908, 733; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (t, $J = 7.5$ Hz, 9H), 1.08 (m, 6H), 1.06 (t, $J = 7.4$ Hz, 3H), 1.93 (m, 2H), 3.79 (s, 1H), 5.31 (s, 2H), 5.33 (d, $J = 16.2$ Hz, 1H). 5.78 (d, $J = 16.2$ Hz, 1H), 7.54 (s, 1H), 7.63 (dd, $J = 7.9$, 6.9 Hz, 1H), 7.92 (d, $J = 7.9$ Hz, 1H), 7.96 (d, $J = 6.9$ Hz, 1H), 8.37 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.4, 7.8, 29.8, 31.6, 50.2, 66.5, 72.8, 97.5, 118.3, 127.5, 127.8, 128.0, 129.1, 131.4, 138.3, 140.2, 147.2, 150.3, 151.2, 153.3, 157.8, 174.0; HRMS *m*/*z* calcd for $C_{26}H_{30}N_2O_4Si$ 462.1975, found 462.1973.

(20*S*)-12-Isopropyldimethylsilyl camptothecin (3d). Using the general procedure B, 7.7 mg of the title compound was prepared from camptothecin (20 mg, 0.057 mmol) in 30% yield as pale yellow solid in addition to recovered camptothecin (19%). $[\alpha]_D^{20} = +62.5$ (c 0.04, CH_2Cl_2); IR 3346 (br), 2945, 2863, 1747, 1657, 1602, 1558, 1486, 1401, 1245, 1223, 1157, 1046, 1002, 909, 841, 767, 732; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.48 (s, 6H), 0.98 (d, $J = 7.4$ Hz, 3H), 1.0 (d, $J = 7.4$ Hz, 3H), 1.06 (t, $J = 7.4$ Hz, 3H), 1.49 (m, 1H), 1.92 (m, 2H), 3.78 (s, 1H), 5.30 (s, 2H), 5.32 (d, $J = 16.2$ Hz, 1H). 5.77 (d, $J = 16.2$ Hz, 1H), 7.52 (s, 1H), 7.62 (dd, $J = 7.9$, 6.8 Hz, 1H), 7.92 (d, $J = 7.9$ Hz, 1H), 7.97 (d, $J = 6.8$ Hz, 1H), 8.37 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −3.8, −3.6, 7.9, 14.0, 18.1, 31.5, 50.2, 66.5, 72.8, 96.2, 118.3, 127.5, 127.8, 128.0, 129.2, 131.4, 137.8, 141.5, 147.1, 150.4, 151.1, 153.1, 157.8, 174.0; HRMS *m*/*z* calcd for $C_{25}H_{28}N_2O_4Si$ 448.1818, found 448.1815.

(20*S*)-12-Cyclohexyldimethylsilyl camptothecin (3g). Using the general procedure B, 7.3 mg of the title compound was prepared from camptothecin (20 mg, 0.057 mmol) in 26% yield as pale yellow solid in addition to recovered camptothecin (10%). $[\alpha]_D^{20} = +33.3$ (c 0.09, CH_2Cl_2); IR 3363 (br), 2918, 2845, 1745, 1657, 1602, 1558, 1486, 1401, 1245, 1223, 1157, 1046, 909, 837, 768, 732; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.46 (s, 6H), 1.07 (t, $J = 7.3$ Hz, 3H), 1.18 (br, 6H), 1.67 (br, 5H), 1.94 (m, 2H), 3.76 (s, 1H), 5.30 (s, 2H), 5.32 (d, $J = 16.2$ Hz, 1H). 5.77 (d, $J = 16.2$ Hz, 1H), 7.56 (s, 1H), 7.62 (t, $J = 7.4$ Hz, 1H), 7.91 (d, $J = 7.4$ Hz, 1H), 7.95 (d, $J = 7.4$ Hz, 1H), 8.36 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −3.4, 7.8, 26.4, 27.1, 28.1, 28.4, 31.5, 50.3, 66.5, 72.8, 97.6, 118.3, 127.5, 127.8, 128.0, 129.1, 131.3, 137.7, 141.6, 147.1, 150.3, 151.1, 153.1, 157.8, 174.2; HRMS *m*/*z* calcd for $C_{28}H_{32}N_2O_4Si$ 488.2131 found 488.2133.

(20*S*)-12-Diethylmethylsilyl camptothecin (3h). Using the general procedure B, 7 mg of the title compound was prepared from camptothecin (20 mg, 0.057 mmol) in 26% yield as pale yellow solid in addition to 10% recovered camptothecin. $[\alpha]_D^{20} = +50.0$ (c 0.05, CH_2Cl_2); IR 3389 (br), 2953, 2874, 1746, 1659, 1602, 1555, 1486, 1402, 1223, 1157, 1046, 1004, 908, 838, 787, 732; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.48 (s, 3H), 0.9–1.1 (m, 13H), 1.96 (m, 2H), 3.79 (s, 1H), 5.31 (s, 2H), 5.33 (d, $J = 16.2$ Hz, 1H). 5.78 (d, $J = 16.2$ Hz, 1H), 7.53 (s, 1H), 7.63 (t, $J = 7.4$ Hz, 1H), 7.92 (d, $J = 7.4$ Hz, 1H), 7.97 (d, $J = 7.4$ Hz, 1H), 8.37 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.5, 6.5, 7.9, 31.6, 50.2, 66.5, 72.8, 97.4, 118.3, 127.5, 127.8, 128.0, 129.2, 131.4, 137.8, 141.0, 147.2, 150.4, 151.1, 153.2, 157.8, 174.0; HRMS *m*/*z* calcd for $C_{25}H_{28}N_2O_4Si$ 448.1818, found 448.1824.

(20*S*)-7-*tert*-Butyldimethylsilyl camptothecin *N*-oxide (4). To a solution of 7-*t*-butyldimethylsilyl camptothecin **2b** (50 mg, 0.11 mmol) in glacial acetic acid (10 mL) was added 30% H_2O_2 (0.8 mL, 7 mmol). This solution was then gently heated at 75 °C for 3 h, then it was evaporated to dryness under reduced pressure. The orange residue was purified by flash chromatography (15% acetone in CH_2Cl_2) on silica gel to give 40.3 mg of 7-*tert*-butyldimethylsilyl camptothecin-*N*-oxide as pale orange powder in 81% yield. $[\alpha]_D^{20} = +10.0$ (c 0.46, CH_2Cl_2); IR 3342 (br), 2933, 2884, 2857, 1750, 1654, 1596, 1557, 1499, 1464, 1258, 1224, 1160, 1090, 821; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.71 (s, 6H), 1.00 (s, 9H), 1.06 (t, $J = 7.2$, Hz, 3H), 1.88 (m, 2H), 5.28 (d, $J = 16.8$ Hz, 1H), 5.32 (s, 2H), 5.72 (d, $J = 16.8$, 1H), 7.69 (t, $J = 7.7$ Hz, 1H), 7.79 (t, $J = 7.8$ Hz, 1H), 8.26 (d, $J = 8.4$ Hz, 1H), 8.40 (s, 1H), 8.84 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −0.2, 0.0, 8.2, 19.8, 27.5, 32.1, 53.4, 66.4, 73.0, 103.1, 119.7, 129.0, 130.2, 130.4, 131.3, 134.9, 136.2, 138.3, 141.0, 141.4, 150.8, 157.2, 173.8, 207.5; HRMS *m*/*z* calcd for $C_{26}H_{30}N_2O_5Si$ 478.1924, found 478.1902.

(20*S*)-10-Hydroxy-7-*tert*-butyldimethylsilyl camptothecin (2a) by photolysis. A 100 mL Pyrex round bottom flask was charged with 7-*tert*-butyldimethylsilyl camptothecin-*N*-oxide **4** (36 mg, 0.075 mmol) and degassed dioxane (30 mL). To this solution was then added 1 N aqueous H_2SO_4 (80 μL, 0.08 mmol). The resulting solution was photolyzed by high pressure Hg lamp for 80 min until the starting material was not observable in TLC. The reaction mixture was then evaporated to dryness, and the residue was purified by flash chromatography (20% acetone in CH_2Cl_2) on silica gel to give 9.8 mg of combined mixture of 7-*tert*-butyldimethylsilyl camptothecin **2b** and unreacted 7-*tert*-butyldimethylsilyl camptothecin-*N*-oxide **4**, and 20.7 mg of the title compound as yellow powder in 58% yield. $[\alpha]_D^{20} = +22.8$ (c 1.89, CH_2Cl_2/MeOH 4:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.68 (s, 6H), 0.96 (s, 9H), 1.03 (t, $J = 7.2$, Hz, 3H), 1.88 (m, 2H), 3.77 (br, 1H), 5.31 (d, $J = 16.2$ Hz, 1H), 5.31 (s, 2H), 5.75 (d, $J = 16.2$, 1H), 7.47 (dd, $J = 9.0$, 1.8 Hz, 1H), 7.61 (d, $J = 1.8$ Hz, 1H), 7.78 (s, 1H), 8.22 (d, $J = 9.0$ Hz, 1H); HRMS (–CO_2) *m*/*z* calcd for $C_{25}H_{30}N_2O_3Si$ 434.2026, found 434. 2009.

(20*S*)-10-Acetoxy-20-*O*-acetyl-7-*tert*-butyldimethylsilyl-camptothecin (7). A mixture of diacetate **6** (12.0 g, 26.8 mmol), *tert*-butyldimethylsilane (12.0 g, 103.2 mmol), *tert*-butyl peroxide (14.4 g, 98.5 mmol), trifluoroacetic acid (9.6 g, 84.2 mmol) and triisopropylsilanethiol (1.2 mL, 5.6 mmol) in 1,4-dioxane (180 mL) was heated at reflux for 30 h under N_2 atmosphere. The light-brown solution was concentrated and 3% aqueous sodium bicarbonate (250 mL) was added to the residue. The

mixture was stirred vigorously for 1 h and filtered. The solid was washed with water (3×50 mL) and petroleum ether (3×50 mL), air-dried, and digested in boiling ether (1200 mL) for 1 h. After cooling to room temperature, the mixture was filtered to recover unreacted starting material **6** (9%) and to isolate (20*S*)-10-acetoxy-20-*O*-acetyl-12-*tert*-butyldimethylsilylcamptothecin **8**. The filtrate was concentrated to give 13.5 g of solid residue, which was chromatographed over silica gel (28×4 cm). The column was eluted with ethyl acetate/petroleum ether (1:9, 1:4, 3:7, 2:3) to remove non-polar impurities and to isolate bis-silyl compound, (20*S*)-10-acetoxy-20-*O*-acetyl-7, 12-bis (*tert*-butyldimethylsilyl)camptothecin **9**. Further elution (1:1, 3:2) gave product-containing fractions, which were pooled and concentrated (aspirator). The residual yellow solid (3.4 g) was re-chromatographed over silica gel (22×3 cm) eluting with methylene chloride/petroleum ether (1:1), methylene chloride and methylene chloride/acetone (19:1, 9:1). Product-containing fractions were pooled and concentrated (aspirator). The yellow solid (3.0 g) was triturated with petroleum ether–ether mixture (4:1, 180 mL) at room temperature for 1 h to afford 2.6 g of compound **7**, mp 266–269 °C (dec.). This material (2.6 g) was re-crystallized from ethyl acetate-petroleum ether to yield 2.1 g of 7-silylated compound **7**, mp 272–275 °C (dec.). A total of 51 g diacetate **6** was silylated in this manner to provide 9.0 g of intermediate **7**.

The once crystallized material (9.0 g) was re-crystallized again from the same solvent to yield 8.3 g (13.0%) of 7-silylated intermediate **7**, mp 274–276 °C (dec.). $[\alpha]_D^{21}$ −20.9 (c = 0.64, CH_2Cl_2); ^{1}H NMR (360 MHz, $CDCl_3$): δ 0.69 (s, 6H), 0.96 (t, *J* = 6.8 Hz, 3H) 0.98 (s, 9H), 2.20 (m, 2H), 2.21 (s, 3H), 2.40 (s, 3H), 5.30 (s, 2H), 5.40 (d, *J* = 17.3 Hz, 1H), 5.68 (d, *J* = 17.3 Hz, 1H), 7.19 (s, 1H), 7.55 (dd, *J* = 9.4 Hz, 2.9 Hz, 1H), 8.11 (d, *J* = 2.2 Hz, 1H), 8.21 (d, *J* = 2.2 Hz, 1H), 8.21 (d, *J* = 9.0 Hz, 1H). Analysis calcd for $C_{30}H_{34}N_2O_7Si$ (562.69): C, 64.04; H, 6.09; N, 4.98. Found: C, 64.04; H, 6.08; N, 4.97.

(20*S*)-10-Acetoxy-20-*O*-acetyl-12-*tert*-butyldimethylsilylcamptothecin (8). A part of the above ether-insoluble material was purified by silica gel column chromatography eluting with 50–90% ethyl acetate in petroleum ether. Product-containing fractions were pooled and concentrated (aspirator). The solid residue was re-crystallized from ethyl acetate–petroleum ether (1:1) to give 0.8 g of pure title compound 8, mp 286–288 °C (dec.). $[\alpha]_D^{21}$ −49.3 (c = 0.34, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): 0.50 (s, 3H), 0.53 (s, 3H), 0.97 (s, 9H), 1.03 (t, *J* = 7.5 Hz, 3H), 2.18 (m, 2H), 2.20 (s, 3H), 2.41 (s, 3H), 5.27 (s, 2H), 5.38 (d, *J* = 17.0 Hz, 1H), 5.69 (d, *J* = 17.0 Hz, 1H), 7.03 (s, 1H), 7.66 (d, *J* = 2.7 Hz, 1H), 7.68 (d, *J* = 2.4 Hz, 1H), 8.31 (s, 1H). Anal. calcd for $C_{30}H_{34}N_2O_7Si$ (562.69): C, 64.04; H, 6.09; N, 4.98. Found: C, 63.84; H, 6.14; N, 4.98.

(20*S*)-10-Acetoxy-20-*O*-acetyl-7, 12-bis (*tert*-butyldimethylsilyl)camptothecin (9). A small amount of the title compound was isolated when the above ether-soluble material was subjected to purification by column chromatography. A few bis-silyl containing fractions were pooled, and concentrated (aspirator). The solid residue (0.7 g) was re-crystallized from ethyl acetate–petroleum ether to give 0.5 g of pure compound **9**, mp 249–251 °C. $[\alpha]_D^{21}$ −33.9 (c = 0.29, CH_2Cl_2); ^{1}H NMR (360 MHz, $CDCl_3$): δ 0.51 (s, 3H), 0.53 (s, 3H), 0.67 (s, 6H), 0.98 (s, 9H), 1.00 (s, 9H), 1.03 (t, *J* = 7.6 Hz, 3H), 2.17 (m, 2H), 2.19 (s, 3H), 2.40 (s, 3H), 5.29 (s, 2H), 5.37 (d, *J* = 17.3 Hz, 1H), 5.69 (d, *J* = 17.3 Hz, 1H), 7.04 (s, 1H), 7.65 (d, *J* = 2.5 Hz, 1H), 8.11 (d, *J* = 2.9 Hz, 1H). Anal. calcd for $C_{36}H_{48}N_2O_7Si_2$ (676.96): C, 63.87; H, 7.15; N, 4.14. Found: C, 63.62; H, 7.03; N, 4.07.

(20S)-7-*tert*-Butyldimethylsilyl-10-hydroxycamptothecin (2a); method A. Diacetate **7** (4.0 g, 7.1 mmol) was dissolved in a mixture of ethanol (360 mL) and concd HCl (40 mL) and the solution heated at reflux for 24 h. The solution was concentrated (aspirator), fresh ethanol (50 mL) was added to the residue, and the solvent was removed. This process of adding ethanol and distilling it off under reduced pressure was repeated two more times. The yellow solid was suspended in water (200 mL). The pH of the mixture was adjusted to ca. 4 with aqueous sodium bicarbonate. The solid was collected by filtration, washed with water (3×25 mL), and air-dried to give 3.4 g of crude product **2a**. Similarly, another 4.2 g of diacetate **7** was hydrolyzed to afford 3.6 g of **2a**. The combined material (7.0 g) was re-crystallized from ethanol-petroleum ether to afford 5.8 g (83.2%) of pure title compound **2a** as a light yellow solid, mp 255–257 °C (dec.). $[\alpha]_D^{21}$ + 28.6 (c = 2.02, CH_2Cl_2/MeOH, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$/CD_3OD): δ 0.62 (s, 6H), 0.91 (s, 9H), 0.96 (t, *J* = 7.6 Hz, 3H), 1.85 (m, 2H), 5.20 (s, 2H), 5.23 (d, *J* = 16.8 Hz, 1H), 5.64 (d, *J* = 16.8 Hz, 1H), 7.33 (dd, *J* = 9.2 Hz, 2.4 Hz, 1H), 7.51 (d, *J* = 2.8 Hz, 1H), 7.58 (s, 1H), 7.97 (d, *J* = 9.6 Hz, 1H). Anal. calcd for $C_{26}H_{30}N_2O_5Si.0.5H_2O$ (487.62): C, 64.04; H, 6.41; N, 5.74. Found: C, 64.14; H, 6.19; N, 5.72.

(20S)-7-*tert*-Butyldimethylsilyl-10-hydroxycamptothecin (2a); method B. Sodium methoxide solution (7.0 g, 2.5 wt%, 3.2 mmol) was added dropwise to a suspension of diacetate **7** (1.3 g, 2.3 mmol) in anhydrous methanol (50 mL) at room temperature. After 4 h, the clear light-brown solution was acidified with glacial acetic acid (0.4 g) and then concentrated (aspirator). The yellow solid was digested in water (50 mL) and collected by filtration to yield 1.1 g of crude title compound **2a**. Similarly, another 0.85 g of diacetate **9a** was hydrolyzed to afford 0.7 g of **2a**. The combined material (1.8 g) was re-crystallized from ethanol-petroleum ether to give 1.3 g (71.1%) of the title compound **2a**.

(20S)-12-*tert*-Butyldimethylsilyl-10-hydroxycamptothecin (3a). A solution of sodium methoxide in methanol (3.8 g, 2.5 wt%, 1.74 mmol) was added drop-wise to a suspension of (20S)-10-acetoxy-20-*O*-acetyl-12-*tert*-butyldimethylsilylcamptothecin (**8**, 0.7 g, 1.24 mmol) in methanol (40 mL) at room temperature under nitrogen atmosphere. The resulting clear light-yellow solution was stirred for 6 h. The solution was acidified to ca. pH 4 by adding a few drops of glacial acetic acid and then concentrated (aspirator). Water (50 mL) was added to the solid residue. After stirring for 30 min, the mixture

was filtered to give 0.6 g of crude product. This material was re-crystallized from ethanol–petroleum ether to afford 0.3 g (50.4%) of pure 12-silyl compound **3a** as a light yellow solid, mp 310 °C (dec.). $[\alpha]_D^{21}+9.0$ (c = 0.38, CH_2Cl_2/MeOH, 4:1); ^1H NMR (300 MHz, $CDCl_3$/CD_3OD): δ 0.53 (s, 3H), 0.54 (s, 3H), 0.96 (s, 9H), 1.04 (t, J = 7.5 Hz, 3H), 1.93 (m, 2H), 5.21 (s, 2H), 5.31 (d, J = 16.2 Hz, 1H), 5.70 (d, J = 16.2 Hz, 1H), 7.15 (d, J = 2.7 Hz, 1H), 7.51 (s, 1H), 7.61 (d, J = 3.0 Hz, 1H), 8.14 (s, 1H). Anal. calcd for $C_{26}H_{30}N_2O_5Si$ (478.62): C, 65.25; H, 6.32; N, 5.85. Found: C, 65.04; H, 6.30; N, 5.79.

(20S)-7,12-Bis (*tert*-butyldimethylsilyl)-10-hydroxycamptothecin (10). A solution of sodium methoxide in methanol (1.8 g, 2.5 wt%, 0.83 mmol) was added dropwise to a suspension of (20S)-10-acetoxy-20-*O*-acetyl-7, 12-bis (*tert*-butyl-dimethylsilyl)camptothecin (**9**, 0.4 g, 0.59 mmol) in methanol (20 mL) at room temperature under nitrogen atmosphere. The resulting clear light-yellow solution was stirred for 6 h. The solution was acidified to ca. pH by adding a few drops of glacial acetic acid and then concentrated (aspirator). Water (50 mL) was added to the solid residue and the mixture was stirred for 30 min. The solid was collected by filtration and air-dried to give 0.3 g of crude product. This material was re-crystallized from ethanol-petroleum ether to afford 0.23 g (65.6%) of pure 7,12-bis-silyl compound **10** as a light yellow solid, mp 310 °C (dec.). $[\alpha]_D^{21}+8.2$ (c = 0.19, CH_2Cl_2/MeOH, 4:1); ^1H NMR (300 MHz, $CDCl_3$/CD_3OD): δ 0.52 (s, 6H), 0.67 (s, 6H), 0.98 (s, 9H), 1.01 (s, 9H), 1.03 (t, J = 7.2 Hz, 3H), 1.92 (m, 2H), 5.28 (s, 2H), 5.31 (d, J = 16.2 Hz, 1H), 5.71 (d, J = 16.2 Hz, 1H), 7.58 (s, 1H), 7.585 (s, 1H), 7.59 (s, 1H). Anal. calcd for $C_{32}H_{44}N_2O_5Si_2.0.4\ C_5H_{10}$ (620.93): C, 65.77; H, 7.79; N, 4.51. Found: C, 65.53; H, 7.79; N, 4.62.

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References and Notes

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