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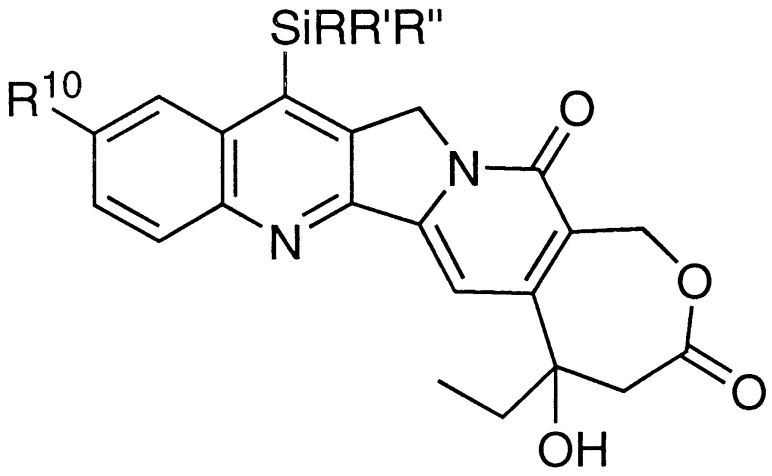

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Solution-Phase Parallel Synthesis of 115 Homosilatecan Analogues

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The parallel synthesis of 115 homosilatecans on 1−5 mg scale has been accomplished. Key reactions include *N*-propargylation of a common iodopyridone lactone with a silyl-substituted propargyl bromide, followed by cascade radical annulation with a substituted isonitrile. Simple manual techniques for parallel reactions were coupled with automated purifications (SPE, HPLC) to give high-purity final products. The speed and simplicity of the automated purification protocol more than compensated for yield losses in the synthesis of some analogues relative to traditional flash chromatographic purifications.

Introduction

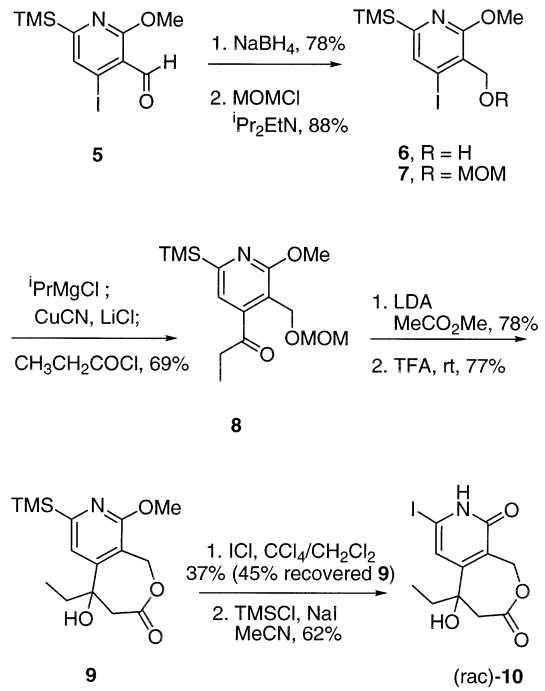
Homocamptothecin **1** (hCPT), prepared by Lavergne and co-workers in 1997, is a novel seven-membered E-ring homologue of the important anticancer agent camptothecin **2** (CPT).[1,2] Ring expansion of the α-hydroxy-δ-lactone E-ring of camptothecin **2** into the β-hydroxy-ϵ-lactone ring of hCPT **1** significantly improves the drug's stability in human plasma. hCPT and several A-ring-substituted analogues have rapidly emerged as promising leads in the field of chemotherapeutic drug design.[3] Because of differences in hCPT-induced DNA cleavage by Topo I compared to camptothecin,[4] it has been proposed that the SAR of camptothecins may not directly apply to homocamptothecins.[3b,c] Structure−activity studies of the hCPT series will thus shed light on the biological mode of action of the homocamptothecin class of antitumor agents.

The cascade radical approach to camptothecins[5] has proved to be very practical and general for synthesis of camptothecin and analogues. 7-Silylcamptothecins **3**, now usually called silatecans, show excellent potential in preclinical assays for further development as therapeutic agents.[6] In 2000, we adapted the radical cyclization approach to camptothecin derivatives to solution-phase parallel techniques and prepared 64- and 48-member libraries of racemic mappicines and mappicine ketones.[7] With this work as a platform, we decided to undertake the solution-phase parallel synthesis of homocamptothecin libraries. Biological studies have shown that the dual 7,10-substitution on camptothecins diminishes binding of the drug carboxylate form to HSA.[8] Indeed, several 10-modified 7-silyl homocamptothecins (**4**, 10-modified homosilatecans) prepared by traditional methods displayed exceptionally high blood stability.[3e] Therefore, we decided to synthesize a homosilatecan library bearing diverse 7-silyl and 10-substituents.

Results and Discussion

Like camptothecin,[9] only one of the two enantiomers of hCPT displays cytotoxic activity.[3b] We have recently reported the first asymmetric total synthesis of hCPT and analogues.[10]

Scheme 1



However, for these early stage of SAR studies, it was more practical to synthesize homosilatecans as racemic mixtures. Our original racemic synthetic route to homocamptothecins[3e] was crafted from our second generation synthesis[5] of camptothecin and Bigg's semisynthesis[1] of hCPT. However, the key Reformatsky reaction used to make the hCPT lactone proved difficult to conduct on a large scale,[11] so a more efficient racemic route was developed.

The new synthetic approach to the key common precursor to hCPT and analogues is shown in Scheme 1. The synthesis of **10** started with 3-formyl-4-iodo-2-methoxy-6-trimethylsilyl pyridine **5**, which is an early intermediate in the total synthesis of CPT.[5] Treatment of iodoformyl pyridine **5** with $NaBH_4$ in EtOH at −40 °C afforded hydroxymethyl pyridine **6** in 78% isolated yield. Alcohol **6** was next protected as its MOM (methoxymethyl) ether[12] to give **7** (88% yield).

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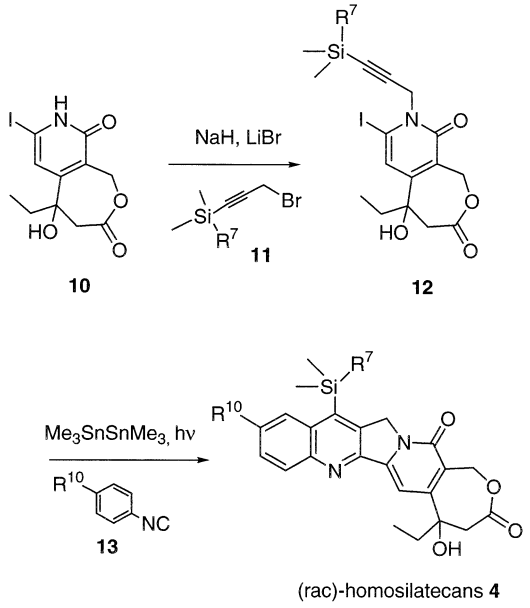
Scheme 2



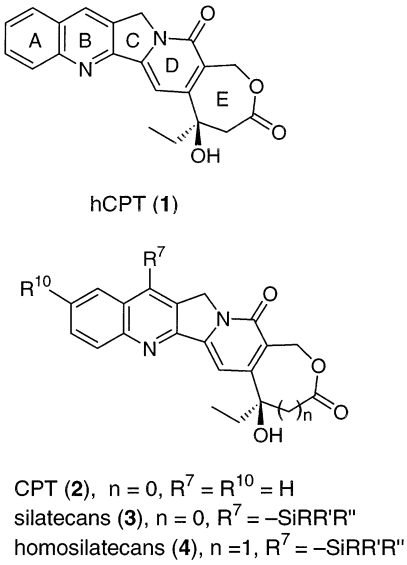


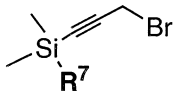
Figure 1. Structures of hCPT, CPT, and analogues.

Making use of Knochel's protocol,[13] treatment of **7** with ^{i}PrMgCl at −40 °C, followed by addition of CuCN/LiCl and quenching of the resulting cuprate reagent with propionyl chloride, provided the key ketone intermediate **8** in 69% isolated yield.[14]

Aldol condensation between ketone **8** and the anion of methyl acetate, generated at −78 °C by using lithium diisopropylamide (LDA), afforded the crude β-hydroxy ester (not shown) in 78% yield. This aldol reaction proved easy to conduct and was reproducible on large scale. Treatment of the crude β-hydroxy ester with TFA at room temperature gave the TMS−lactone **9** (77% yield). At this stage, the standard two-step sequence[3e] completed the preparation of iodolactone **10**. Iodinative desilylation of TMS−lactone **9** was executed with ICl in CH_2Cl_2/CCl_4 to afford an iodolactone in 37% yield along with 45% of recovered TMS−lactone **9**, which was stored for later reuse. Demethylation was accomplished by addition of TMSCl to a mixture of the iodolactone and NaI in CH_3CN, providing iodopyridone **10** in 62% yield.

The preparation of 7,10-modified homosilatecans was next envisioned via a two-step protocol shown in Scheme 2 that entails (1) parallel N-alkylation of the iodopyridone **10** with

Table 1. Propargyl Bromide Building Blocks



11{1-13}

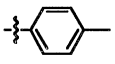
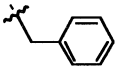
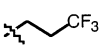
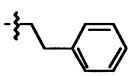
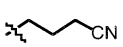
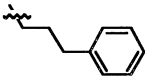
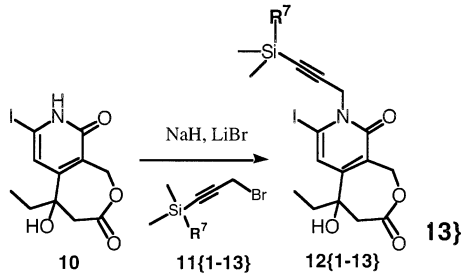
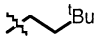
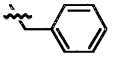
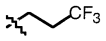
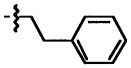
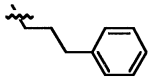
Straight Hydrocarbon Chain		Branched Hydrocarbon Chain		Aromatic Chain	
R^7 = Me	**11{1}**	R^7 = 	**11{6}**	R^7 = Ph	**11{9}**
	**11{2}**		**11{7}**		**11{10}**
	**11{3}**		**11{8}**		**11{11}**
	**11{4}**				**11{12}**
	**11{5}**				**11{13}**

Table 2. Parallel Synthesis of N-Alkylated Iodopyridones



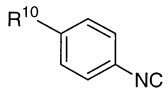
R^7	Isolated Yield (%)	R^7	Isolated Yield (%)	R^7	Isolated Yield (%)
Me[a]	49 **12{1}**		50 **12{6}**	Ph	54 **12{9}**
	53 **12{2}**		59 **12{7}**		53 **12{10}**
	44 **12{3}**		51 **12{8}**		55 **12{11}**
	43 **12{4}**				65 **12{12}**
	39 **12{5}**				51 **12{13}**

several propargyl bromides **11** and (2) parallel radical annulation of N-propargylated iodopyridones **12** with a collection of isonitriles **13**.

As a logical extension of our work in the generation silatecans,[15] propargyl bromide building blocks **11**{*1*−*13*}[15] (Table 1) were chosen. On the basis of the nature of the R^7 group on silicon, the propargyl bromides are divided into three classes: straight chain hydrocarbons **11**{*1*−*5*}, branched hydrocarbons **11**{*6*−*8*}, and aromatic rings **11**{*9*−*13*}. These bromides were readily prepared by silylation of the THP ether of propargyl alcohol, followed by bromination.[15]

With the goal of exploring effects of electron withdrawing, electron-releasing and hydrogen-bonding groups on the 10 position, aryl isonitriles **13**{*1*−*7*}[5,6] were selected as partners (Figure 2). Homosilatecans prepared by the use of **13**{*6*} (OAc) and **13**{*7*} (NHBoc) can be deprotected to give homosilatecans with R^{10} = OH and NH_2, respectively.

To make N-propargylated iodopyridones **12**, two or three N-alkylation reactions were run in parallel. Each solution of iodopyridone **10** (150−200-mg scale) in a 4:1 mixture of DME/DMF was treated with NaH at 0 °C.[16] After 15 min, flame-dried LiBr was added. The mixtures were then stirred at room temperature for 15 min before the corresponding propargyl bromides were added. The reaction mixtures were then heated concurrently in an oil bath at 65 °C for 20 h. After workup, the crude reaction mixtures were concentrated under reduced pressure and chromatographed on silica gel to provide the radical precursors **12**{*1*−*13*} in 39−65% yield. Table 2 shows the structures and isolated yields of the 13-member N-propargylated iodopyridone family made in this semiparallel fashion.



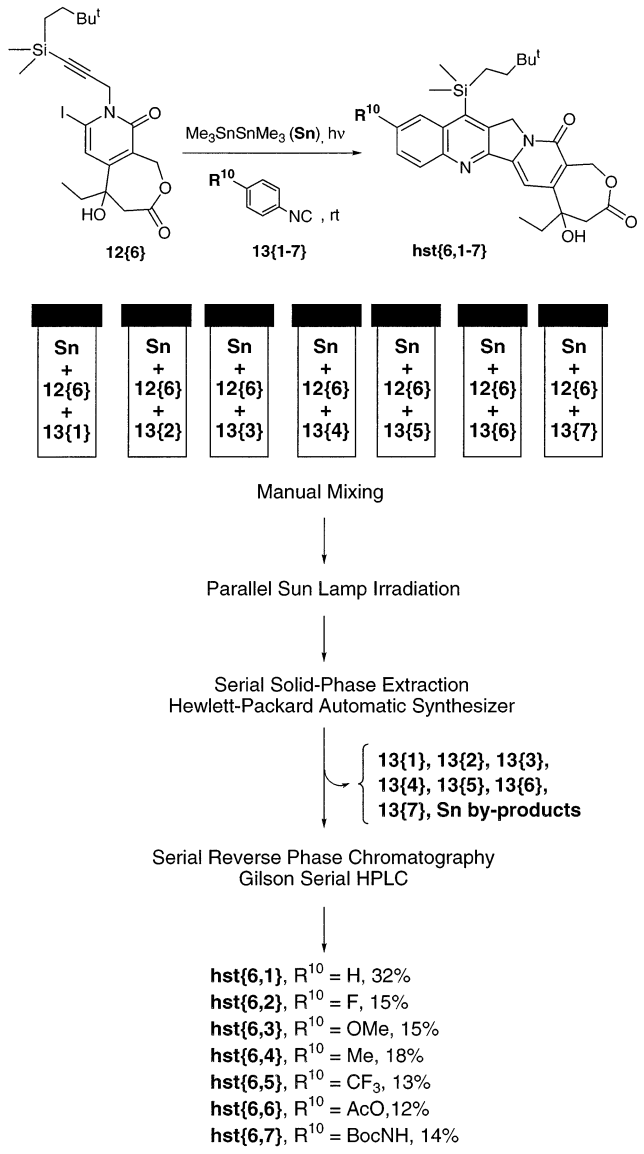
13

13{1}, R^{10} = H
13{2}, R^{10} = F
13{3}, R^{10} = OMe
13{4}, R^{10} = Me
13{5}, R^{10} = CF_3
13{6}, R^{10} = AcO
13{7}, R^{10} = BocNH

Figure 2. Isonitrile reagent building blocks.

With N-propargylated iodopyridones and isonitriles in hand, the library synthesis of homosilatecans was next pursued.[17] In a typical run, an iodopyridone **12** was reacted in parallel with seven different isonitriles, and the crude products were subsequently purified in an automated fashion. To illustrate the process, the procedure for parallel synthesis of homosilatecans **hst**{*6,1*−*7*}—the first library members to be synthesized—is described (Scheme 3). About 10 mg of the iodopyridone **12**{*6*} was placed in each of seven vials along with 0.4 mL of benzene. Because a deprotection step followed the radical reaction with either *p*-AcO-phenylisoni-

Scheme 3



trile **13**{*6*} or *p*-BocNH-phenylisonitrile **13**{*7*}, these cascade radical reactions were run with 2 times more iodopyridone than that used for the other phenylisonitriles **13**{*1*−*5*}. One of the seven different isonitriles **13**{*1*−*7*} (3 equiv) was added to each of the seven solutions of iodopyridone **12**{*6*}. Isonitriles **13**{*1*−*6*} were added via syringe as 1 M solutions in benzene. In contrast, isonitrile **13**{*7*} is a solid and was simply weighted into the vial. Following addition of 2.0 equiv of $Me_3SnSnMe_3$ to each reaction mixture, the seven vials were next irradiated simultaneously at room temperature with a 275-W GE sunlamp for 1.5 h.

After irradiation, the seven reaction mixtures were concentrated to dryness by a programmed sequence for automated evaporation on a Hewlett-Packard (HP) 7686 automatic synthesizer.[18] A stream of nitrogen gas served to evaporate the reaction solvent, a process that took ∼20 min per vial. After completion, the seven crude residues were diluted with CH_2Cl_2, and then a two-step automated purification protocol followed. Solid-phase extraction using the HP7686 synthesizer preceded preparative reversed-phase chromatography using a Gilson serial HPLC.[6]

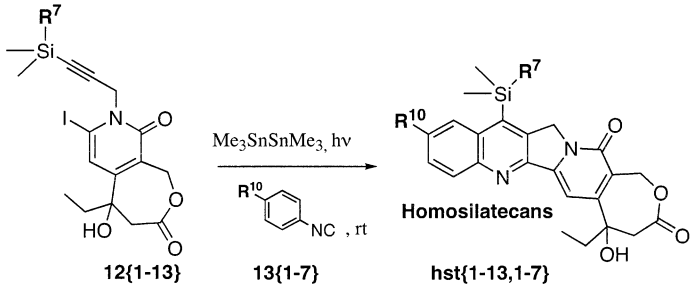
The programmed sequence for solid-phase extraction allowed smooth separation of excess isonitrile, polymerized isonitrile, and tin byproducts from each product homosilatecan. The robot liquid handler first loaded each crude solution onto a prepacked Hewlett-Packard 300-mg silica gel cartridge. Elution with CH_2Cl_2 and then a 99:1 mixture of CH_2Cl_2/acetone removed excess isonitrile and tin impurities. Subsequent elution with a 3:1 mixture of CH_2Cl_2/acetone provided the product fractions. The whole automated solid-phase extraction sequence took ∼1 h per sample, so the seven reactions were robotically purified overnight. Because of the large difference in polarity between the homosilatecan products and the byproducts, the automated solid-phase extraction protocol provided clean products, as judged by TLC analysis. However, to ensure high purity of the homosilatecans, the products isolated from the solid-phase extraction were next purified by automated high performance liquid chromatography on a Symmetry C_{18} column attached to a Gilson serial HPLC using an acetonitrile/water gradient system (see Supporting Information) to give the seven products in the isolated yields shown in Scheme 3.

The isolated yields of the first seven homosilatecans prepared in parallel and purified in an automated fashion ranged from 12 to 32%, as shown in Scheme 3. LC/MS analysis (negative APCI) of **hst**{*6,1*−*7*} showed in each case the presence of a single molecular ion peak corresponding to the $[M - H]^+$ ion of the expected homosilatecan. The lowest yielding product, **hst**{*6,6*}, was also assayed by ^1H NMR spectroscopy, and no impurities were evident. Even though the isolated yields were low to moderate, a "high-speed" protocol for the synthesis of pure homosilatecans in parallel fashion had been successfully developed. Adequate amounts for biological testing, 2 mg on average, were obtained.

With this 1 × 7-sized array as a prototype, the preparation of three larger libraries was next undertaken. These are grouped as libraries 1, 2, and 3 on the basis of the nature of the R^7 substituent on the $SiMe_2R^7$ group by analogy to the classification previously used for iodopyridones **12**. Tables 3−5 show the C7 and C10 substituents, isolated yields and names (**hst**{*x,y*}, *x* = iodopyridone reagent **12**{*1*−*13*}, *y* = isonitrile reagent **13**{*1*−*7*}) for all homosilatecans prepared in these arrays. Typically, the synthesizer was programmed to purify 7 samples at a time.[19] Likewise, the serial HPLC was programmed to purify 7−14 samples overnight. For yield comparison purposes, homosilatecans **hst**{*2,4*}, **hst**{*3,6*}, and **hst**{*4,4*} were withdrawn at random and purified by traditional flash chromatography; isolated yields were 45, 49, and 32%, respectively.

Calculating from the relevant entries in Tables 3−5, the isolated yields of homosilatecans with a straight hydrocarbon, an aromatic, and a branched hydrocarbon silyl side chain averaged 25, 40, and 20%, respectively. Isolated yields of homosilatecans upon automated purification were, thus, lower than those of the three homosilatecans purified by traditional flash chromatography (45, 49, 32%). To ascertain whether low yields were due to the radical reaction itself or to the automated purification protocol, some of the lowest-yielding analogues were reprepared and

Table 3. Library 1: Homosilatecans Bearing a Straight Hydrocarbon R Chain[a]



	R^{10} = H	F	OMe	Me	CF_3	AcO	BocNH
R^7 = Me[b]	61 **hst{1,1}**	49 **hst{1,2}**	44 **hst{1,3}**	47 **hst{1,4}**	49 **hst{1,5}**	29 **hst{1,6}**	Np **hst{1,7}**
	31 **hst{2,1}**	35 **hst{2,2}**	22 **hst{2,3}**	45[b] **hst{2,4}**	6 **hst{2,5}**	27 **hst{2,6}**	26 **hst{2,7}**
	32 **hst{3,1}**	6 **hst{3,2}**	16 **hst{3,3}**	24 **hst{3,4}**	22 **hst{3,5}**	49[b] **hst{3,6}**	12 **hst{3,7}**
	42 **hst{4,1}**	19 **hst{4,2}**	20 **hst{4,3}**	32[b] **hst{4,4}**	16 **hst{4,5}**	9 **hst{4,6}**	10 **hst{4,7}**
	16 **hst{5,1}**	11 **hst{5,2}**	5 **hst{5,3}**	8 **hst{5,4}**	9 **hst{5,5}**	7 **hst{5,6}**	3 **hst{5,7}**

[a] Top: % isolated yield. [b] Isolated yield from flash column chromatography on silica gel. [c] Np = Not prepared.

Table 4. Library 2: Homosilatecans Bearing a Branched Hydrocarbon R Chain[a]

	R^{10} = H	F	OMe	Me	CF_3	AcO	BocNH
R^7 =	32 **hst{6,1}**	15 **hst{6,2}**	15 **hst{6,3}**	18 **hst{6,4}**	13 **hst{6,5}**	12 **hst{6,6}**	14 **hst{6,7}**
	26 **hst{7,1}**	27 **hst{7,2}**	17 **hst{7,3}**	8 **hst{7,4}**	25 **hst{7,5}**	13 **hst{7,6}**	37 **hst{7,7}**
	11 **hst{8,1}**	12 **hst{8,2}**	19 **hst{8,3}**	7 **hst{8,4}**	22 **hst{8,5}**	19 **hst{8,6}**	10 **hst{8,7}**

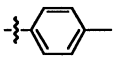
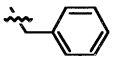
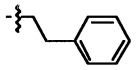
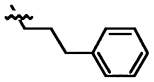
[a] Top: % isolated yield.

purified by regular flash chromatography. Specifically, homosilatecans **hst**{*2,5*} (6%), **hst**{*3,2*} (6%), **hst**{*5,7*} (3%), **hst**{*7,4*} (8%), and **hst**{*8,4*} (7%) were synthesized again and purified by conventional chromatography on silica gel. The traditional purification afforded these homosilatecans in 32, 54, 57, 45, and 52% yields, respectively. These improved yields clearly show that the reduced yields in the library synthesis were caused by the purification protocol, and we suspect that the automated SPE is the point of material loss.

Each library member was obtained in 1−5-mg scale and was characterized by automated LC/MS analysis. In some cases, the peak in the LC/MS chromatogram was broad. Nevertheless, MS detection showed the presence of a single parent ion, which confirmed the identity of each prepared homosilatecan. In addition, **hst**{*1,5*}, **hst**{*2,2*}, **hst**{*4,1*}, **hst**{*5,7*}, **hst**{*6,6*}, **hst**{*7,4*}, **hst**{*8,6*}, **hst**{*9,2*}, **hst**{*10,7*}, and **hst**{*11,4*} library members were chosen at random and characterized by standard spectroscopic techniques (^{1}H NMR, LRMS, and HRMS). The Supporting Information contains copies of the LC/MS and spectroscopic data.

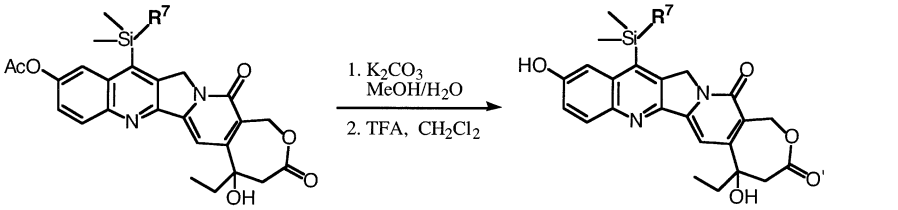
As further extension of this solution-phase parallel synthetic approach, deprotections of the previously prepared 10-AcO and 10-BocNH homosilatecan library members were undertaken. With only an average of 3 mg of 10-AcO and 10-BocNH homosilatecans in hand, the crude products were

Table 5. Library 3: Homosilatecans Bearing an Aromatic R Chain[a]

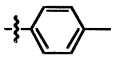
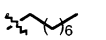
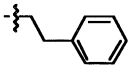
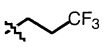
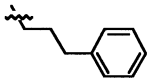
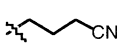
	R^{10} = H	F	OMe	Me	CF_3	AcO	BocNH
R^7 = Ph	19 **hst{9,1}**	18 **hst{9,2}**	10 **hst{9,3}**	46 **hst{9,4}**	23 **hst{9,5}**	33 **hst{9,6}**	56 **hst{9,7}**
	22 **hst{10,1}**	10 **hst{10,2}**	9 **hst{10,3}**	14 **hst{10,4}**	39 **hst{10,5}**	19 **hst{10,6}**	47 **hst{10,7}**
	57 **hst{11,1}**	52 **hst{11,2}**	34 **hst{11,3}**	53 **hst{11,4}**	51 **hst{11,5}**	36 **hst{11,6}**	36 **hst{11,7}**
	57 **hst{12,1}**	43 **hst{12,2}**	60 **hst{12,3}**	38 **hst{12,4}**	62 **hst{12,5}**	34 **hst{12,6}**	41 **hst{12,7}**
	64 **hst{13,1}**	33 **hst{13,2}**	46 **hst{13,3}**	23 **hst{13,4}**	43 **hst{13,5}**	20 **hst{13,6}**	37 **hst{13,7}**

[a] Top: % isolated yield.

Table 6. Parallel Synthesis of 10-OH-Homosilatecans[a]



10-A(10-AcO-Homosilatecan 10-OH-Homosilatecan atecan

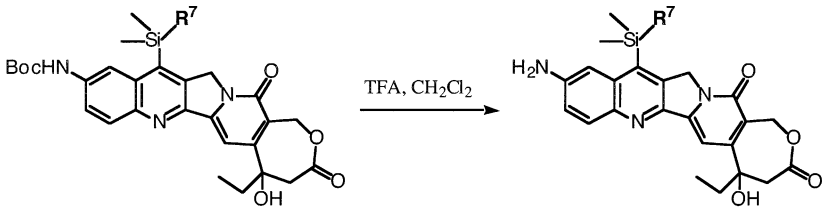
R^7	R^{10} = OH	R^7	R^{10} = OH	R^7	R^{10} = OH
Me	46 **hst{1,8}**		50 **hst{6,8}**	Ph	14 **hst{9,8}**
	57 **hst{2,8}**		54 **hst{7,8}**		29 **hst{10,8}**
	49 **hst{3,8}**		50 **hst{8,8}**		38 **hst{12,8}**
	74 **hst{4,8}**				46 **hst{13,8}**
	65 **hst{5,8}**				

[a] Top: % isolated yield.

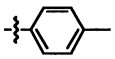
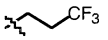
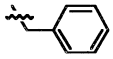
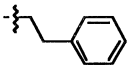
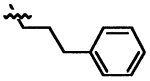
purified by traditional flash chromatography on silica gel. Tables 6 and 7 show the structures and isolated yields of the different 10-hydroxy[20] and 10-amino homosilatecans, respectively, that were made by a parallel method.

In a general procedure for deacetylation, two to four homosilatecans were treated in parallel with 4 equiv of K_2CO_3 in a 1:1 MeOH/H_2O mixture at room temperature for 2 h. Under such basic conditions, some of the lactone

Table 7. Parallel Synthesis of 10-NH_2-Homosilatecans[a]



10-I 10-BocNH-Homosilatecan 10-NH_2-Homosilatecan

R^7	$R^{10} = NH_2$	R^7	$R^{10} = NH_2$	R^7	$R^{10} = NH_2$
	55 **hst{2,9}**		70 **hst{6,9}**	Ph	29 **hst{9,9}**
	42 **hst{3,9}**		68 **hst{7,9}**		10 **hst{10,9}**
	47 **hst{4,9}**		67 **hst{8,9}**		61 **hst{11,9}**
	55 **hst{5,9}**				59 **hst{12,9}**
					65 **hst{13,9}**

[a] Top: % isolated yield.

hydrolyzes.[10] Thus, following concentration of the crude mixtures, the residues were dissolved in a 2:1 CH_2Cl_2/TFA mixture and stirred at room temperature for 4 h to ensure relactonization. After flash chromatography, isolated yields were low (14%) to moderate (74%), averaging 48% (Table 6).

Similarly, parallel Boc deprotections (2−4 at a time) were run. Thus, treatment of all 12 10-BocNH-homosilatecans with TFA in CH_2Cl_2 (1:2, v:v) at room temperature for 1−24 h[21] allowed for the cleavage of the Boc group. After purification of the crude products by flash chromatography, the isolated yields of 10-NH_2-homosilatecans ranged from 10 to 70%, averaging 52% (Table 7).

All homosilatecans within these two series were characterized by LC/MS analysis. ^{1}H NMR spectra were also recorded for two of these analogues, **hst**{*3,8*} and **hst**{*13,9*}. The ^{1}H NMR spectra were clean, and mass spectral data (negative APCI MS detection) obtained on an LC/MS instrument were also satisfactory.

Conclusions

A practical and efficient synthetic strategy to the homocamptothecin class of antitumor agents has been developed. This strategy has been used for the combinatorial preparation of several homosilatecan libraries. In total, 115 new analogues were prepared, and each final sample was individually purified by HPLC. The low solubility or variable polarity of some of the hCPT analogues probably accounts for the low isolated yields of certain homosilatecan library members as a result of losses in the automated SPE. Nevertheless, the speed of the parallel route offsets the sacrifice in yield and provides milligram quantities of all target products. Biological evaluation of these homosilatecans is currently in progress and may lead to the design and synthesis of analogues possessing better blood stability and antitumor activity than those of the natural product CPT. Finally, the results provide further confirmation of the scope and generality of the cascade radical annulation approach to camptothecin and mappicine; ∼1000 analogues of these molecules have been made in recent years by traditional, parallel, and mixture[22] synthesis methods, with only one reported failure.

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Supporting Information Available. Experimental procedures and characterization data for all new compounds (82 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) 7-TMS derivatives **hst**{*1,1−7*} (Table 3) were purified by flash chromatography on silica gel. During the radical reactions of the TMS-propargylated iodopyridone **12**{*1*}, the homosilatecan products were observed to precipitate out as they formed; thus, a difficult and low-yielding automated purification protocol was foreseen.

(20) **hst**{*11,8*} was accidentally lost; thus, this member is not included in Table 6.

(21) Reactions were followed by TLC analysis, and individual reaction times are given in the Supporting Information.

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