

A General Synthetic Approach to the (20*S*)-Camptothecin Family of Antitumor Agents by a Regiocontrolled Cascade Radical Cyclization of Aryl Isonitriles

Hubert Josien, Sung-Bo Ko, David Bom, and Dennis P. Curran*

Abstract: A general and efficient synthesis of (20*S*)-camptothecin (**1a**) is reported. A key common intermediate containing the pyridone and lactone (DE) rings of camptothecin and most derivatives was constructed from 2-trimethylsilyl-6-methoxypyridine by a series of metalation reactions and a Heck cyclization to provide an achiral bicyclic enol ether. Sharpless asymmetric dihydroxylation followed by lactol oxidation and iododesilylation produced the key intermediate in 94% enantiomeric excess. Alkylation with prop-

argyl bromide and a cascade radical reaction with phenyl isonitrile then produced **1a**. About 20 other penta- and hexacyclic analogues of camptothecin with differing single or multiple substituents at C7, C9, C10, C11, and/or C12 were made by changing the propargylating agent and the isonitrile. Included among these are sever-

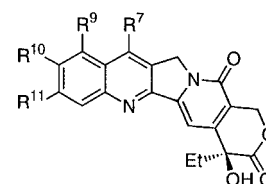
al drug candidates and the approved drugs topotecan and irinotecan. The synthesis of the prodrug irinotecan is a direct one that does not pass through the active metabolite. The use of *ortho*-trimethylsilyl-substituted isonitriles allows the regioselective synthesis of camptothecin analogues in cases where isomeric mixtures are formed from the parent isonitriles. The synthesis of the derivatives relies on the broad scope and functional group tolerance of the key cascade radical reaction.

Keywords: alkaloids • antitumor agents • camptothecins • cascade reactions • radical reactions

Introduction

First isolated by Wall and Wani in 1966, (20*S*)-camptothecin (**1a**) and its derivatives have resurfaced during the last decade as some of the most promising agents for the treatment of solid tumors by chemotherapy (Figure 1).^[1] This family of topoisomerase poisons^[2] acts by interfering with the unwinding of supercoiled DNA by the cellular enzyme topoisomerase I, an enzyme which is overexpressed in malignant cells. In replicating cancer cells, the formation of a ternary complex of topoisomerase I, DNA, and camptothecin triggers a cascade of events leading to apoptosis and programmed death.^[3]

The initial clinical trials of camptothecin were hampered by its poor water solubility and the attendant problems with administration,^[4] but more recent structure–activity studies have identified many compounds with improved solubility and better antitumor activity.^[5] A reasonably detailed picture of the structure–activity relationship of the camptothecin family is now available. In general, substitution on rings C, D, and E is not well tolerated. But substituents on rings A and B



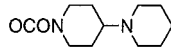
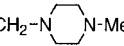
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|--------------------------------------|--|
| 1a Camptothecin | $R^7, R^{11} = H$ |
| 1b 9-Aminocamptothecin (9-AC) | $R^7, R^{10}, R^{11} = H; R^9 = NH_2$ |
| 1c Topotecan™ (TPT) | $R^7, R^{11} = H;$ |
| 1d Irinotecan™ (CPT-11) | $R^9 = CH_2NMe_2; R^{10} = OH$
$R^7 = Et; R^9, R^{11} = H;$ |
| 1e GI-147211C | $R^{10} =$ 
$R^7 = CH_2-N$  $-Me$
$R^9 = H; R^{10}, R^{11} = OCH_2CH_2O$ |

Figure 1. Camptothecin and some clinically important derivatives.

especially at C7, C9, and C10 (and to some extent C11) often show good biological activity and improved physical or pharmacological features. Derivatives such as topotecan (TPT, **1c**)^[6] and irinotecan (CPT-11, **1d**)^[7] have passed through clinical trials and are now being used in several

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countries for treatment of solid tumors. Other compounds such as 9-aminocamptothecin (9-AC, **1b**)^{1b} and GI-147211C (**1e**)⁸ show significant potential. These molecules have proven to be effective against a wide array of refractory solid tumors and seem particularly promising for the treatment of slow-dividing cancer-lines when administered either alone or in combination therapies.^{1,9}

In parallel developments, new formulations have improved biodistribution and drug stability, and this has opened new therapeutic opportunities for poorly soluble camptothecins.¹⁰ The renewed importance of the camptothecin family has stimulated the investigation of new routes to camptothecin and its derivatives.^{11,12}

Several years ago, we initiated a program whose goal was the development of a practical synthesis of camptothecin and derivatives by a radical cascade cyclization. The field of cascade reactions (also sometimes called tandem, domino, or sequential reactions) has undergone an explosive development in recent years.¹³ The best cascade reactions rapidly provide molecular diversity and complexity with minimum amounts of solvents, reagents, energy, and waste. Cascade radical reactions are prized for their capability to build complex, highly substituted ring systems and for their general tolerance of functional groups. The development of new cascade radical reactions continues at a vigorous pace.¹⁴

In 1992, we communicated a first-generation synthesis of racemic camptothecin that featured as its key step a unique [4+1] radical annulation/cyclization between phenyl isonitrile (**2**) and bromopyridone **3** (Scheme 1).¹⁵ The strategy was inspired by a new cascade radical reaction discovered by our group.¹⁶ Although the synthesis was efficient and short

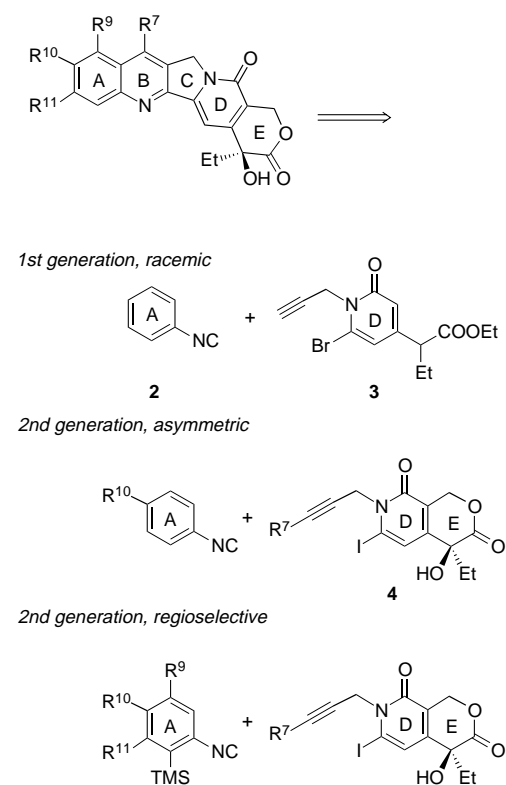
(8 steps), it suffered from two major problems: the hydroxylation at C20 with O₂ yielded racemic camptothecin,¹⁷ and the harsh conditions required for the introduction of the E ring severely restricted the ability to incorporate substituents on the A and B rings. We therefore revised our synthetic plan to incorporate the E ring in the iodopyridine **4** prior to the radical cascade reaction (Scheme 1). The essence of this second-generation synthesis of **1a** has recently been communicated.¹⁸

In this article we describe some key foundation experiments and then give full details of the scope of this second-generation synthesis of camptothecin and an assortment of known and new derivatives. Among the more important new developments are the expansion of the chemistry to encompass new substituents and substituent combinations, the introduction of the first route to enantiomerically pure 7-azacamptothecins, and the development of the first direct total synthesis of the prodrug irinotecan. Prior syntheses of this molecule are all indirect and pass through the active (and therefore toxic) metabolite. We then move to address a fundamental problem that arises in the synthesis of many types of analogues: how can the regiochemical outcome of the radical cyclization with *meta*-substituted aryl isonitriles be controlled? The importance of A ring substituents on antitumor activity makes this a crucial question⁵ and the strategy that we have implemented relies on the introduction of a TMS group on the aryl isonitrile. This substituent acts as a directing group which can be removed after the cascade reaction (Scheme 1, regioselective). As it currently stands, this second-generation synthesis has good efficiency and superior generality, both of which features descend directly from the key radical cascade.

Results and Discussion

The retrosynthetic plan for **1a** is depicted in Figure 2. The plan calls for an assembly of camptothecin in the last step of the synthesis by reaction of *N*-propargyl halopyridine **5** and phenyl isonitrile (**2**) in the radical cascade to construct the B and C rings. In this plan, pyridone **6** becomes a key common synthetic intermediate which can be directed to many camptothecin derivatives by varying the nature of the propargylating agent and the isonitrile in the last two steps. The construction of the α -hydroxylactone moiety of the radical precursor **6** relies on a Sharpless asymmetric dihydroxylation (AD)¹⁹ of enol ether **7**, which was predicted from prior model studies.^{20,21} In turn, the precursor **7** for the AD reaction comes from an intramolecular Heck cyclization. Concurrent with our AD model studies²⁰ Fang and co-workers^{12f} applied a related Heck/AD sequence to a synthesis of camptothecin by a modification of Comins' route.^{12g} Work by Comins and co-workers on successive *ortho*-metalations of pyridines^{12g} provided the foundation for the synthesis of **7** from methoxypyridine **8**.

The first task was the seemingly small problem of choosing a halogen for the radical precursor. This issue was raised because during the early stages of this work Comins communicated a synthesis of camptothecin that passed through the



Scheme 1. First- and second-generation radical cascade reactions.

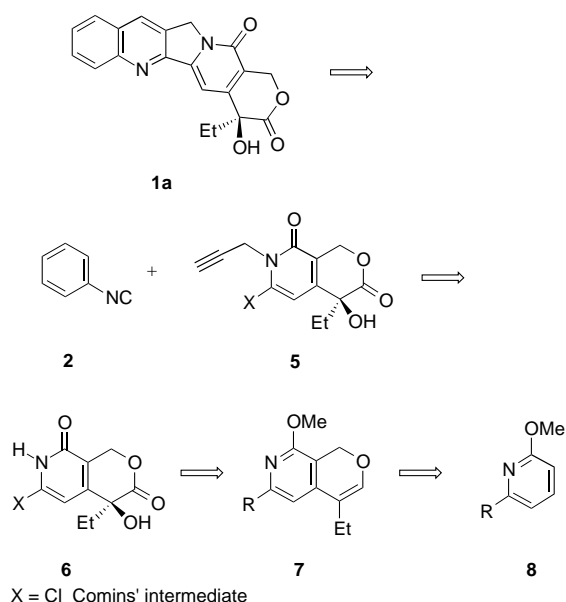


Figure 2. Retrosynthetic analysis of (20S)-camptothecin.

chloride derivative of **6**.^[12g] The key chlorine atom that attracted our attention actually served as a protecting group for a proton during deprotonation reactions that were performed in Comins' synthesis. Prior to that, we had only used bromides as radical precursors;^[15,16] however, it was evident that if chlorides were useful, we could simply employ the first part of Comins' synthesis and use his intermediate for our purposes. To probe this possibility, several 6-halo-2-pyridones **9** were prepared by selective *N*-alkylation^[22] of 6-halo-2-pyridone^[15e] and their reactions with aryl isonitriles **2** or **10** were evaluated (Table 1).

Most of the reactions were carried out following the optimized radical cascade conditions: a 0.05M benzene solution of the radical precursor, 3 equiv of aryl isonitrile, and 1.5 equiv of hexamethylditin were irradiated with a sunlamp or a UV lamp for 18–24 h.^[15e] As shown in Table 1, the yield of **11** was strongly dependent on the halide. The chloro derivative **9a** was essentially useless, giving no tetracyclic product under most conditions, including the standard ones (entry 1). However, with **10** a poor yield of **11b** was isolated when Cossy's conditions were applied (entry 2).^[23] By comparison, reaction with bromopyridone **9b** afforded **11a** in a yield comparable to that of the first-generation synthesis with pyridone **3** (57%, entry 3). By far the best result was obtained with iodopyridone **9c**, which yielded tetracycle **11a** in an excellent yield when reacted with **2** (entry 4). Clearly an iodide is the precursor of choice.

In more detailed model studies described elsewhere,^[15e] we learned that an allyl group could be substituted for the propargyl group

(the intermediate product is presumably air-oxidized). This result, together with some recent observations of 1,5-hydrogen-atom-transfer reactions in aryl radicals,^[24] led us to attempt a radical translocation approach with vinyl bromide **12**.^[25] Unfortunately, no tetracyclic product was formed in this reaction (entry 5), and labeling experiments with Bu₃SnD showed that the proposed 1,5-hydrogen transfer did not occur.

These results appeared to preclude the use of Comins' chloride **6** (X = Cl) in the synthesis of **1a**. This conclusion was confirmed when the Glaxo group kindly provided us with a sample of this intermediate. Propargylation yielded **13**, the reaction of which under the standard radical conditions did not provide any spot corresponding to camptothecin on an analytical TLC plate (entry 6). Since the detection of camptothecin on TLC by UV light is highly sensitive, we can conclude that no camptothecin was formed in this reaction.

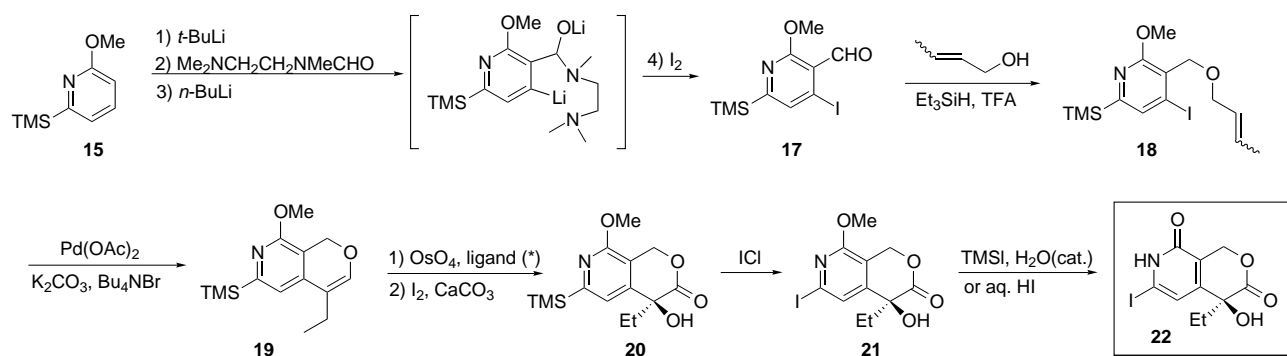
Thus the DE fragment **6** (X = I) became the key target. Intermediate **7** could not be prepared directly from an iodide precursor **8** (R = I) using Comins' chemistry since several *ortho*-metalation steps are involved.^[12g] Recent work by Snieckus and co-workers has emphasized the role of silicon moieties as protective groups in metalation chemistry.^[26] Arylsilanes are stable to alkylolithium reagents and can be removed by various electrophiles through *ipso* substitution.^[27] In particular, iododesilylation is a popular method for the generation of iodides from aryl- or alkenylsilanes.^[28]

Accordingly, 2-methoxy-6-trimethylsilylpyridine (**15**) was prepared from 2-bromo-6-methoxypyridine (**14**) by means of halogen-metal exchange followed by addition of chlorotri-

Table 1. Synthesis of tetracycles **11a,b** from various 6-substituted-2-pyridones and isonitriles.

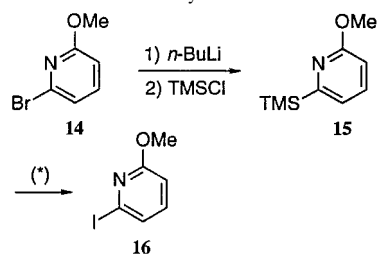
	Pyridone	Isonitrile	Product	Conditions	Yield 11 (%)
1		10	11b	Me ₆ Sn ₂ , C ₆ H ₆ , sun lamp	0
2	9a X = Cl	10	11b	Et ₃ N, CH ₃ CN, UV lamp	10
3	9b X = Br	2	11a	Me ₆ Sn ₂ , C ₆ H ₆ , sun lamp	57
4	9c X = I	2	11a	Me ₆ Sn ₂ , C ₆ H ₆ , sun lamp	80
5		2	11a	Me ₆ Sn ₂ , C ₆ H ₆ , sun lamp	0[a]
6		2	1a	Me ₆ Sn ₂ , C ₆ H ₆ , sun lamp	0

[a] The same result was obtained with AIBN–Bu₃SnH, syringe pump addition. With AIBN–Bu₃SnD on **12** only, the vinyl bromide was reduced (D was not incorporated in the pyridone system). [b] Prepared from Comins' chloride **6** (X = Cl)^[12g] after *N*-propargylation.^[22]

Scheme 2. Synthesis of **22** (see Table 3).

methylsilane. In order to investigate the possibilities for iododesilylation reactions of **15**, the model reactions shown in Table 2 were conducted. Silane **15** was completely consumed on reaction with I_2 ,^[28c] but the reaction required high temperature and resulted in low yield (entry 1). Addition of $AgBF_4$

Table 2. Model study for TMS–iodine exchange.



Conditions (*)	Ratio 16:15 (Yield 16 , %)
1 I_2 , ^[a] 30 h	> 30:1 (17)
2 I_2 , $AgBF_4$, MeOH, 24 h	< 30:1 (0)
3 NaI, NCS, AcOH	< 30:1 (0)
4 NIS/TfOH, CH_2Cl_2 , 48 h	< 30:1 (0)
5 IDLP, CH_2Cl_2/CCl_4 , 48 h	< 30:1 (0)
6 ICl, CH_2Cl_2 , 48 h	1:1 (n.d.)
7 ICl, CH_3CN , 48 h	2.5:1 (47)
8 ICl, CH_2Cl_2/CCl_4 2:1, 48 h	2:1 (56)

[a] Reaction carried out at 80 °C.

was not beneficial (entry 2). Iodonium sources such as iodonium dilutidine perchlorate (IDLP),^[29] NIS-TfOH,^[30] or NaI-NCS^[30] proved unreactive and **15** was recovered (entries 3–5). In the end, the best result was obtained by treating **15** with ICl.^[28b–e] In CH_2Cl_2/CCl_4 this reagent gave a reasonable yield of iodopyridine **16** along with recovered starting material (entry 8). Attempts to drive this reaction to completion by using extended reaction times or excess ICl (up to 10 equiv) generally provided **16** in lower yield, and little or no **15** was recovered. The use of a CH_3CN/CCl_4 mixture proved better than CH_3CN alone (entries 6–7). Also, the reaction was not influenced by addition of K_2CO_3 ,^[28d] KF ,^[28e] or amines (data not shown). These data may reflect a competition between the iododesilylation and the formation of an iodopyridinium salt (resulting in ring deactivation).

With this moderately successful iododesilylation procedure in hand, we then proceeded to the synthesis of the DE-

fragment **22** (**6** with $X = I$, Scheme 2).^[18] Directed lithiation ($tBuLi$, THF, $-78^\circ C$) of pyridine **15** followed by addition of *N*-formyl-*N,N,N'*-trimethylethylenediamine yielded an α -amino alkoxide. This intermediate was further deprotonated in situ ($nBuLi$, $-30^\circ C$) and the resulting dianion was trapped with iodine to afford the iodoaldehyde **17** in 49% yield. A reductive etherification^[14f,31] of **17** with crotyl alcohol, triethylsilane (Et_3SiH), and trifluoroacetic acid (TFA) then provided the crotyl ether **18** in 63% yield. After an intramolecular Heck reaction under Grigg's conditions ($Pd(OAc)_2$, K_2CO_3 , Bu_4NBr),^[14f,32] the enol ether **19** was obtained in 69% yield.

This enol ether was then subjected to the Sharpless AD conditions (0.2% mol OsO_4 , AD-mix- β , $MeSO_2NH_2$, 1% mol ligand) and the resulting α -hydroxyketal was further oxidized with iodine and $CaCO_3$ to provide the α -hydroxy lactone **20**. In this sequence, the AD^[19] proved to be strongly influenced by the nature of the ligand used in the reaction (see Scheme 2 and Table 3). The dihydroquinidine-1,3-phthalazinediyl ligand, (DHQD-PHAL), provided **20** in good yield but poor enantiomeric excess (*ee*) (entry 1). The *ee* increased dramatically when the reaction was carried out with the DHQD-pyridine (DHQD-PYR) ligand and the product was isolated in 87% yield and 94% *ee* (entry 2). The (*S*) configuration in **20** was predicted from Sharpless's studies^[19] and our model reactions^[20] and was later confirmed by the synthesis of **1a**. By comparison, the dihydroquinine-PYR (DHQ-PYR) ligand provided the (*R*) isomer in similar yield and *ee* (entry 3).

Table 3. Ligands and yields for compound **20**.

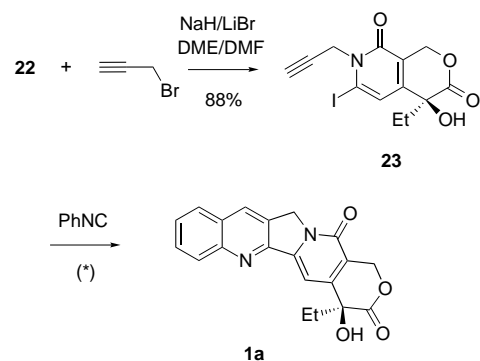
Ligand	Product	Yield(%)	<i>ee</i> (%) ^[a]
1 (DHQD) ₂ -PHAL	20 (<i>S</i>)	87	32
2 (DHQD) ₂ -PYR	20 (<i>S</i>)	87	94
3 (DHQ) ₂ -PYR	20 (<i>R</i>)	84	90

[a] Enantiomeric excess determined by NMR shift experiments with $[Eu(hfc)_3]$.

In the subsequent steps, **20** was subjected to ICl-mediated iodolactonization to provide the iodolactone **21** in 47% yield. As with the model study the reaction did not proceed to completion, but the product could be easily separated from the unreacted material by chromatography, and the latter was recovered in 45% yield. Finally demethylation, with either

aqueous HI or iodotrimethylsilane generated in situ, afforded the key DE fragment **22** in good yield (72%).

With **1a** now only two steps away, **22** was *N*-propargylated to give the radical precursor **23** in 88% yield (Scheme 3 and Table 4). Under these previously optimized conditions,^[22] the tertiary hydroxy group was not affected. The final radical cascade reaction was then performed by irradiating a solution of **23**, phenyl isonitrile (**2**, 3 equiv), and hexamethylditin (1.5 equiv) in benzene at 70 °C with a 275 W sunlamp. To our delight, **1a** crystallized directly from the reaction mixture and was isolated in 63% yield and over 95% *ee* after filtration of the reaction mixture and washing of the residue with diethyl ether (entry 1, Scheme 3 and Table 4). A reaction carried out



Scheme 3. Syntheses of **1a** (see Table 4).

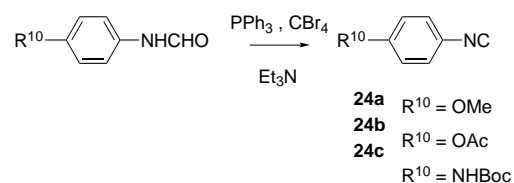
Table 4. Conditions for the radical cascade reaction for the formation of **1a**.

Conditions (*)	Yield 1a
1 Me ₆ Sn ₂ , C ₆ H ₆ , sun lamp, 70 °C, 8 h	63
2 Me ₆ Sn ₂ , <i>t</i> -BuOH, sun lamp, 70 °C, 8 h	45
3 Me ₆ Si ₂ , C ₆ H ₆ , sun lamp, 75 °C, 8 h	52
4 (Me ₃ Si) ₄ Si, C ₆ H ₆ , UV lamp, 75 °C, 30 h	57

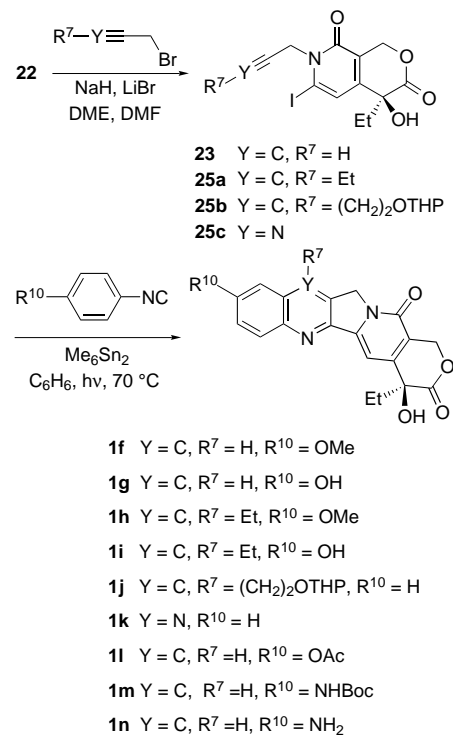
in *tert*-butanol provided **1a** in 45% yield (entry 2). Tin residues are toxic and usually difficult to separate from the products of the reaction. We therefore investigated silane additives in place of ditin.^[33] As shown in Scheme 3, hexamethyldisilane afforded **1a** with a penalty of about 10% yield relative to the ditin counterpart (compare entries 3 and 1), whereas tetrakis(trimethylsilyl)silane^[33b] provided **1a** in 57% yield (entry 4). This last result, obtained only after most of the other work in this paper was completed, suggests that tetrakis(trimethylsilyl)silane may be a useful substitute for hexamethylditin in the syntheses of (20*S*)-camptothecin derivatives described below.

From this second-generation synthesis of **1a**, we then proceeded to evaluating the generality of the method. Several 4-substituted phenyl isonitriles (**24a–c**) were prepared from the corresponding free amines through classical methods,^[34a] or from the *N*-formanilide by using a slight modification of Ziehn's procedure (Scheme 4).^[34b] In parallel, several other *N*-substituted pyridones **25a–d** were synthesized by standard *N*-propargylation, *N*-allylation, or *N*-cyanomethylation of **22**, as shown in Scheme 5.

Combinations of the appropriate isonitriles and iodopyridones provided **1a** (from the allyl precursor **25d**) and the several other derivatives shown in Scheme 5 and Table 5. The



Scheme 4. Synthesis of aryl isonitriles.



Scheme 5. Synthesis of camptothecin analogues.

Table 5. Scope of the radical cascade.

	Radical Precursor	Isonitrile	Product 1 (Yield, %)
1	23	24a	1f (51)
2	25a	24a	1h (57)
3	25b	2	1j (52)
4	25c	2	1k (54)
5	23	24b	1l (63)
6	23	24c	1m (58)
7		2	1a (21)

radical cascade proved to be very tolerant of substituents either on the B ring (from the iodopyridone) or on the A ring (from the isonitrile) and provided in each case 50–60% yield of (20*S*)-camptothecin derivatives. In addition to the free hydroxyl group and the reactive lactone present in all radical precursors, other unaffected groups include tetrahydropyran (THP, entry 3), acetate (entry 5), and carbamate (entry 6). In the last example, the Boc protecting group was easily cleaved from **1m** to provide (20*S*)-10-aminocamptothecin (**1n**), a very active derivative.^[1b]

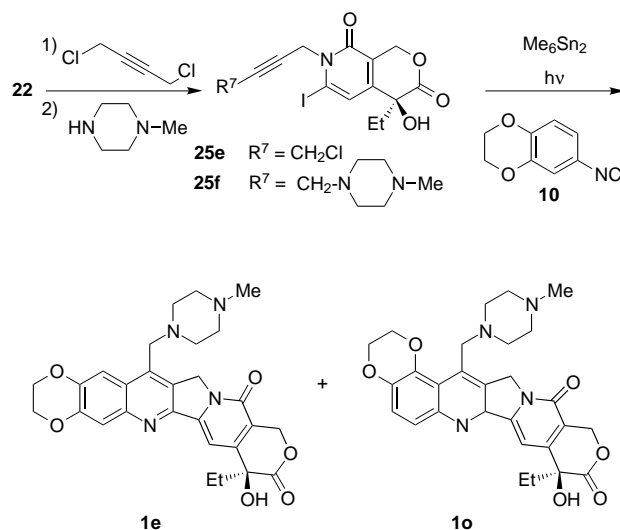
On the reactivity front, a particularly interesting result was obtained with the cyanomethylpyridone **25c**, which provided (20*S*)-7-azacampthothecin (**1k**) in good yield (entry 4). This nuclear analogue of camptothecin was known as a racemate but had not been synthesized before in its enantiomerically pure form.^[5f] *N*-Allylpyridone **25d** provided **1a** through initial 5-*exo*-trig cyclization and subsequent oxidation (presumably by air), but in lower yield (entry 7) than that from the *N*-propargyl derivative. This result was expected from our previous model studies.^[15e]

We also applied this method to the synthesis of the useful intermediates **1g** and SN-38 (**1i**), which are the immediate precursors of the drug **1c** and the prodrug **1d**, respectively. In both cases, the cascade transannulation of iodopyridone with 4-methoxyphenyl isonitrile (**24a**) provided acceptable yields of the camptothecin derivatives (entries 1, 2). Demethylation with aqueous HBr then generated **1g** (which is converted to **1c** by aminomethylation) and **1i** (which is converted to **1d** by acetylation).^[18] Alternatively, **1g** could be obtained by base-mediated deacetylation of **1i**.

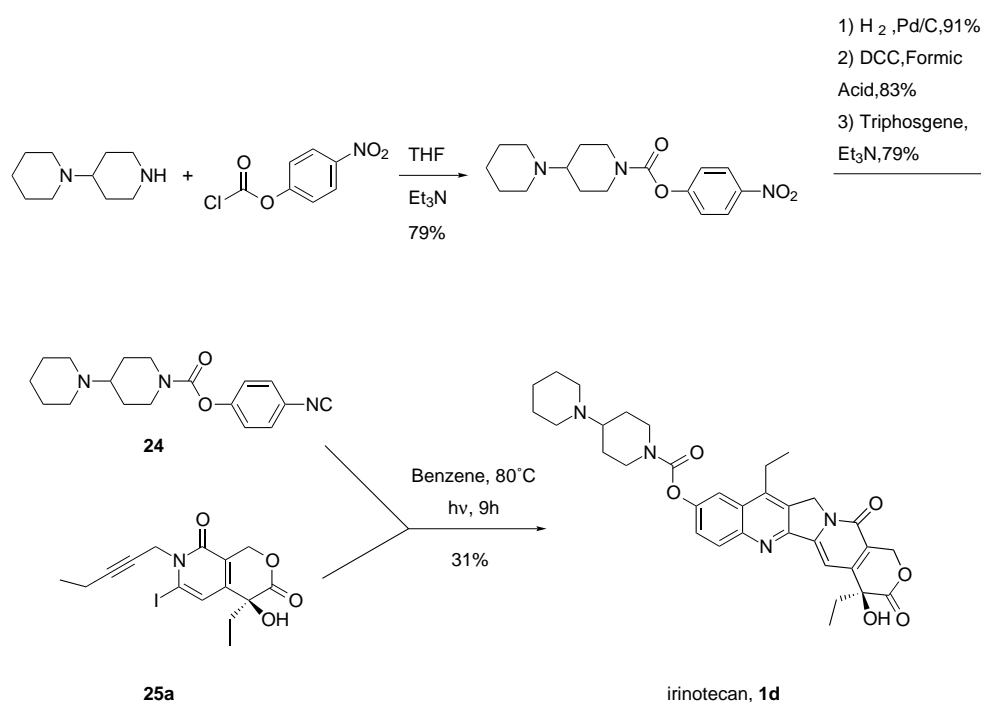
In an especially important application, a direct synthetic approach to irinotecan (**1d**) was also developed as summarized in Scheme 6. All prior approaches to this molecule pass through the intermediate of the active metabolite **1i**. However, not only is this route indirect, in addition the toxicity of **1i** detracts from this type of approach. The requisite isonitrile

yield since the crude yield and purity of this product were very similar to those of the other examples in Table 5.

Scheme 7 shows the synthesis of GI-147211C (**1e**), a potent new camptothecin analogue introduced by Glaxo.^[8] **1e** is one of the most complex camptothecin analogues prepared to date, and the semisynthesis of this compound from **1a** does



Scheme 7. Synthetic route to **1e** and **1o**.



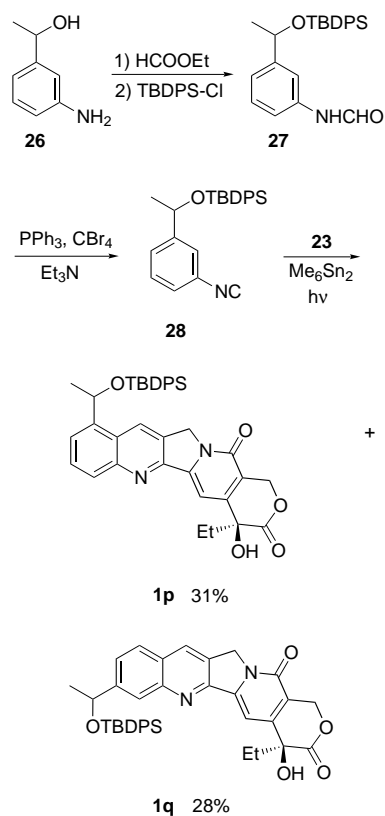
Scheme 6. Synthesis of irinotecan, **1d**

bearing the pyrrolidinyl pyrrolidine prodrug functionality of **1d** was readily available, as shown in Scheme 6. Reaction of this intermediate with the appropriate lactone pyridone **25a** provided **1d** in 31% purified yield. Owing to the presence of basic tertiary amine, **1d** was purified by reverse-phase chromatography. This may have caused a reduction in isolated

not appear to be a viable option. The chemistry shown in Scheme 7 nicely illustrates both the scope and a critical limitation of the isonitrile cascade approach. Following the usual sequence, the radical precursor **25f** was prepared by *N*-alkylation of iodopyridone **22** with 1,4-dichlorobutylene to give the intermediate **25e**. This was then followed by addition of *N*-methylpiperazine to yield **25f**. When this was further reacted with 3,4-ethylenedioxyphenyl isonitrile (**10**),^[34a] an inseparable 60/40 mixture of **1e** and the 9,10-ethylenedioxy regioisomer **1o** was obtained. Leaving the regioselectivity flaw aside, this reaction is a prime example

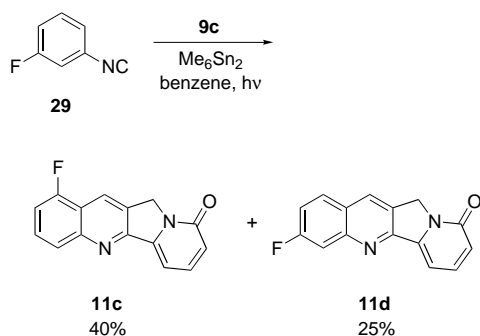
of the power of the isonitrile cascade strategy. Although **1e** is considerably more complex than camptothecin, its synthesis is essentially identical in length to that of camptothecin, and requires only a variation of the reagents in the last two steps. Both tertiary amines and the ethylene dioxy group survived the radical reaction conditions.

The regioisomeric mixture results because the last radical cyclization is not selective; addition occurs almost indiscriminately to both *ortho*-positions of the isonitrile. As described earlier, this problem of regioselectivity with *meta*-substituted isonitriles is general and the selectivity is only slightly influenced by the nature of the substituents.^[16] For example, aryl isonitrile **28**, which bears a relatively large substituent, was prepared from 3-(1-hydroxyethyl)aniline (**26**) through *N*-formylation, alcohol protection, and dehydration.^[34b,35] When this intermediate was reacted with iodopyridone **23**, the radical cascade proceeded to provide the product **1p** of *ortho*-cyclization in 31% yield together with the minor isomer **1q** (from *para*-cyclization) in 28% (Scheme 8). Electronic con-



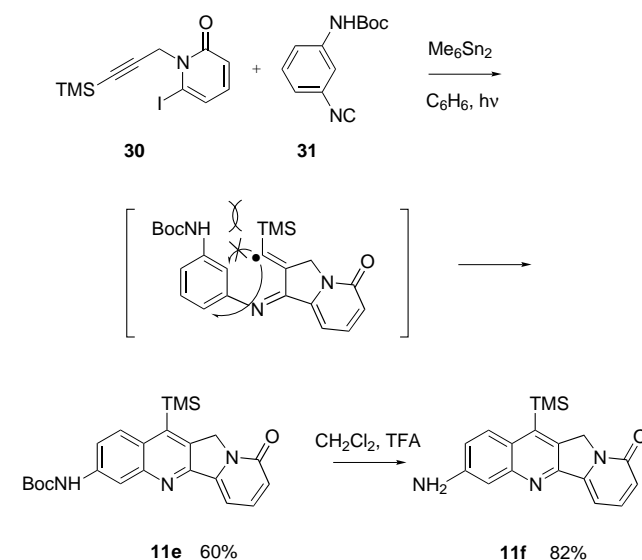
Scheme 8. Synthetic route to **1p** and **1q**.

trol is also largely absent. The model radical reaction with 3-fluorophenyl isonitrile (**29**)^[34a] provided **11c** and **11d** in 40% and 25% yields, respectively (Scheme 9).



Scheme 9. Synthetic route to **11c** and **11d**.

At this stage, we had in hand a synthesis of camptothecin itself along with ready access to any analogue possessing a symmetry plane through the isonitrile group of the aryl isonitrile. Through the use of *para*-substituted isonitriles, many C10-substituted camptothecin derivatives are readily available. Wide scope is also permitted at C7 (the propargyl substituent). However, a selective route to important C9- and C11-substituted derivatives was lacking. To date, we have discovered only one regioselective reaction of a *meta*-substituted isonitrile, but this is an especially important one and it is depicted in Scheme 10. Radical [4+1] annulation of



Scheme 10. Synthetic route to **11e** and **11f**.

iodopyridone **30**^[15c] and aryl isonitrile **31** (prepared from the Boc-amino protected formamide according to Scheme 4) occurred smoothly and provided, after deprotection of the Boc group on **11e**, tetracycle **11f** to the exclusion of its regioisomer. This result is in contrast to that with the aryl isonitrile **28** in the camptothecin series in Scheme 8. In this case, the regioselectivity of the radical cascade may result from repulsion between the NHBoc and TMS groups in the final cyclization. While this solution is not general, it is important because the amino group can readily be diazotized and further converted to a number of C11 derivatives. This approach is less direct than having the desired C11 substituent on the isonitrile, but this is compensated for by a rough doubling of the yield in the radical cyclization step, since a single isomer is formed rather than a mixture of two.

Seeking a more general route to C9- and/or C11-substituted derivatives, we proposed the strategy depicted in Figure 3. The idea was to block one of the reaction sites of the isonitrile with a temporary group which could be removed after the radical reaction. The trimethylsilyl group was chosen since this group can be smoothly removed by fluoride or other protodesilylation methods.^[27,36]

The very robust (20*S*)-9-methylcamptothecin (**1s**)^[1] was selected as a simple candidate to test the validity of this notion; its synthesis is shown in Scheme 11. The requisite

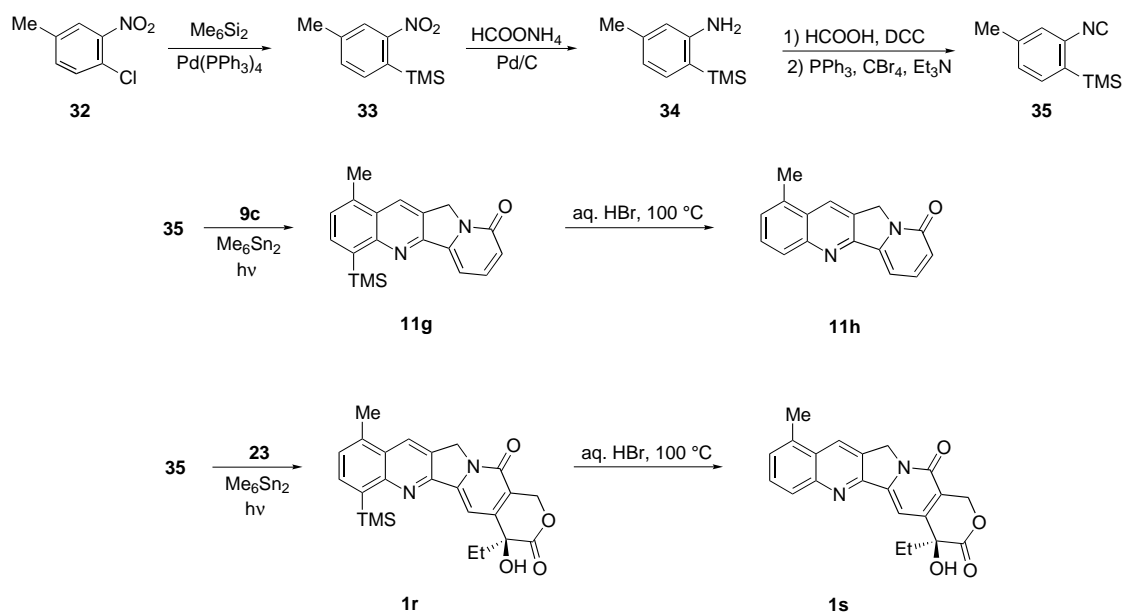
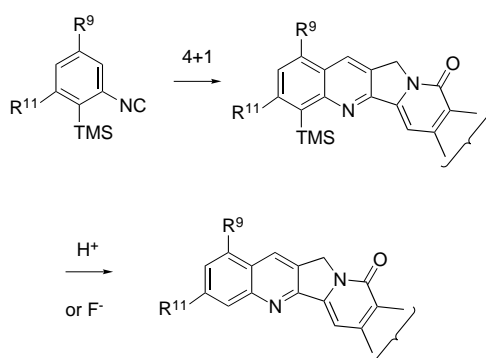
Scheme 11. Synthetic route to **11h** and **1s**.

Figure 3. Regiocontrol in the radical cascade.

isonitrile **35** was prepared in four steps starting from 4-chloro-3-nitrotoluene (**32**). A Pd⁰-catalyzed cleavage of hexamethyldisilane^[37] with **32** provided nitroarylsilane **33** in 64 % yield. This intermediate was reduced quantitatively under classical conditions^[38] and the resulting free amine **34** was formylated with formic acid/dicyclohexylcarbodiimide (DCC)^[39] followed by dehydration^[34b] to provide **35** in 90 % yield.

The radical cascade of the model pyridone **9c** with **35** proceeded very cleanly to give a single isomeric tetracycle **11g** in 46 % yield. This intermediate was easily protodesilylated with aqueous HBr to afford the 9-methyl-substituted tetracycle **11h**. In the camptothecin series, radical reaction between **35** and **23** gave **1r** in 50 % yield. Removal of the TMS group provided **1s** in 85 % yield.

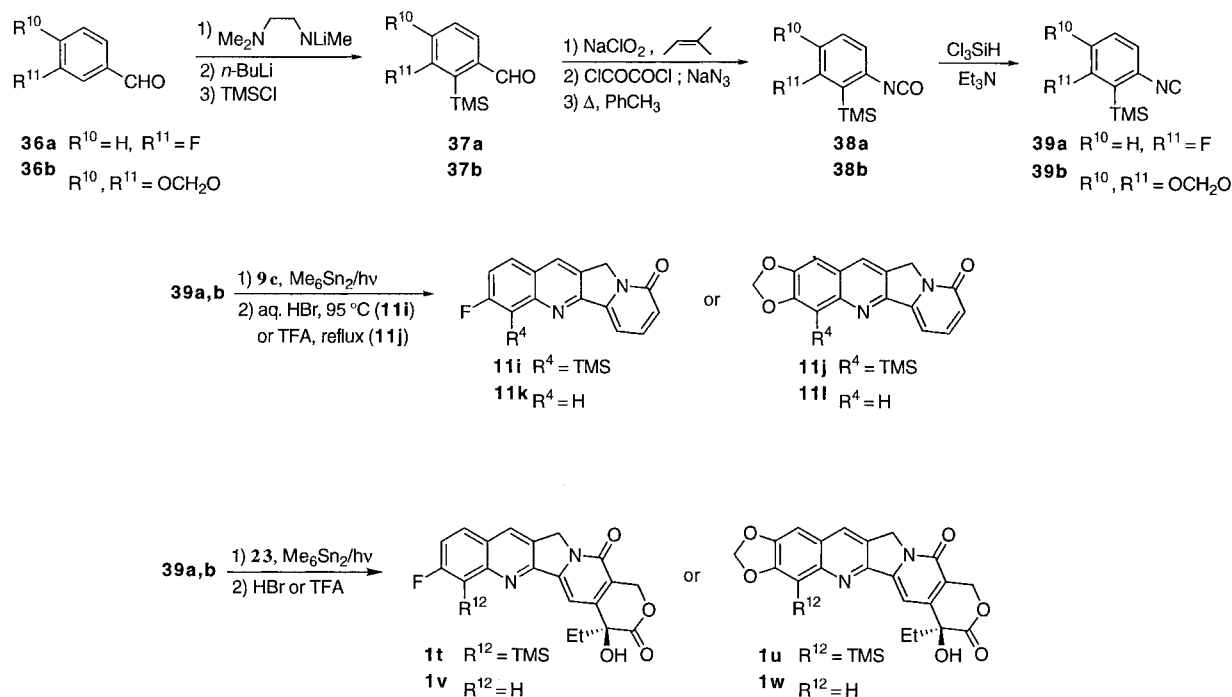
Having established that the *ortho*-TMS group serves admirably for regiocontrol in the C9-substituted series, we then turned our attention to the other *meta*-substitution pattern, which should provide C11-substituted camptothecins. Although large C11 substituents are detrimental to antitumor activity, substitution of the C11 position with small groups such as oxygen or fluorine can result in a remarkable increase in activity.^[1,5] Promising drug candidates such as GI-147211C (**1e**)^[8] and DX-8951f^[5b] have emerged from this trend.

In this context (2*S*)-11-fluorocamptothecin (**1v**) and (2*S*)-10,11-methylenedioxcamptothecin (**1w**) were chosen as good examples (Scheme 12); both compounds are active, and **1w** is one of the most active camptothecin analogues known. The requisite TMS-substituted isonitriles (**39a,b**) were synthesized in a straightforward fashion. *ortho*-Metalation of the α -aminoalkoxide generated from the lithium salt of *N,N,N'*-trimethylethylenediamine and 3-fluorobenzaldehyde (**36a**) or piperonal (**36b**) was followed by the addition of chlorotrimethylsilane to provide aldehydes **37a** and **37b** in 83 % and 51 % yield, respectively.^[40] In these reactions both fluorine- and oxygen-directed metalations provided the expected regioisomer in >95:5 selectivity (as shown by NMR analysis of the crude product). After oxidation of the aldehydes to the free acids^[41] and transformation to the corresponding acyl azides,^[42] a Curtius rearrangement provided the isocyanates **38a** and **38b** in 78 % and 90 % yield, respectively.^[43,44] Deoxygenation^[45] then provided the isonitriles **39a** and **39b** in 66 % and 68 % yield, respectively.

The model reaction of **39a** with **9c** proceeded very smoothly to give one single regioisomer, tetracycle **11i**, in 57 % yield. Similarly the radical reaction with isonitrile **39b** afforded **11j** in 59 % yield. The TMS group in both compounds was removed easily by acid treatment, either with aqueous HBr or trifluoroacetic acid, and the resulting tetracycles **11k** and **11l** were obtained in excellent yields (75 % and 100 %, respectively). Synthesis of camptothecin analogues **1v** and **1w** followed the same series of reactions; **39a** and **39b** provided radical adducts **1t** and **1u** in 64 % and 53 % yield, respectively. Removal of the TMS group then afforded the expected camptothecin derivatives **1v** and **1w** in good yield.

Conclusions

Our first-generation synthesis of camptothecin combined an A-ring isonitrile with a D-ring pyridone in the key cascade radical reaction (A + D \rightarrow ABCD). The lactone ring (E) was



Scheme 12.

then added. The second-generation synthesis reported herein first builds a DE-ring pyridone/lactone and then propargylation and the cascade radical reaction with the isonitrile ring (A) completes the synthesis ($A + DE \rightarrow ABCDE$). In both cases, the BC pyrrolopyridine segment of the molecule is constructed in the radical cascade. The two rings are formed in a sequence of a radical addition followed by two cyclizations that features a powerful if unusual geminal bond formation (most radical cascades have only vicinal bond forming reactions). The scope of the radical cascade and its functional group tolerance is indicated by the fact that we have been able to prepare more than fifty different examples in the course of this work.^[15c]

The second-generation synthesis has several advantages over its predecessor. First, the strategy is inherently more convergent. The early introduction of the E-ring lactone is a crucial feature that reduces the synthesis of derivatives down to as few as two steps (depending on the derivative substitution pattern) from the key intermediate **22**. Even more important than this factor is the functional group tolerance of the second-generation synthesis; the harsh conditions required for lactone introduction in the first-generation route were intolerant of most types of interesting substituents; in effect only camptothecin itself could be made. Also, the new synthesis uses a simple catalytic method, the Sharpless asymmetric dihydroxylation, to introduce the requisite stereocenter prior to the divergence to make derivatives.

Last, and perhaps most important, the strategy is ideally suited to the known structure–activity relationship of the camptothecin family. Rings D and E are relatively intolerant of substitution, and accordingly most of the synthetic steps are spent constructing the invariant DE pyridone/lactone fragment. In the last two key steps, *N*-propargylation affords a

ready and diverse source of C7 substituents (as well as a possible nuclear substitution of carbon for nitrogen), and the radical annulation of the aryl isonitrile provides the C9–C12 substituents. These substituents are ultimately derived from commercially available or readily prepared aniline derivatives. The report of about 20 penta- and hexacyclic camptothecin analogues in this paper, all prepared in enantiomerically pure form by total synthesis, attests to the ease of derivative preparation.

At present, this synthesis is neither the shortest nor the most efficient synthesis of camptothecin.^[12] However, camptothecin is itself not a candidate for clinical treatment of cancer and now serves primarily as a starting material for synthesis of other derivatives. As far as we know, total synthesis of camptothecin is not yet competitive with isolation for large-scale production. From this perspective, the total synthesis of camptothecin itself is largely an academic pursuit and the body of existing work provides an important yardstick with which to measure all new syntheses.

However, the ability to synthesize camptothecin is not the only and now perhaps not even the most important yardstick. We must now ask how well a synthesis produces important existing analogues of camptothecin and whether it has the scope to produce new analogues. These are challenging questions because the important existing analogues are quite diverse. Also most of the simple analogues of camptothecin have been made over the years, so a new synthesis is useful only if it can make more complex ones. We believe that our synthesis has the potential to compete with existing routes to many important camptothecin analogues, whether these routes are by total synthesis or semisynthesis. Perhaps more importantly, the route has allowed us to move further away from known analogues of camptothecin by introducing new substituents as well as by combining known substituents in

new ways. A number of the new derivatives that we have prepared are considerably more active than camptothecin and have activities comparable with the best compounds in the field. These results will be reported in the near future.^[17]

Experimental Section

General: All reactions were run under an argon atmosphere in flame-dried glassware unless otherwise noted. Tetrahydrofuran (THF) and benzene (PhH) were freshly distilled from sodium/benzophenone. Toluene (PhCH₃), methylene chloride (CH₂Cl₂), *N,N*-dimethylformamide (DMF), dimethoxyethane (DME), and triethylamine (Et₃N) were distilled from CaH₂.

2-Methoxy-6-trimethylsilylpyridine (15): 1.6 N *n*BuLi in hexanes (37.5 mL, 60 mmol) was added to a solution of 2-bromo-6-methoxypyridine (11.28 g, 60 mmol) in THF (120 mL) at -78°C . After 1 h at -78°C , chlorotrimethylsilane (8.10 mL, 63 mmol) was added and the resulting mixture was allowed to warm to room temperature. The solution was poured into H₂O (200 mL) and extracted with Et₂O (2 \times 100 mL). The combined organic layers were washed with brine, dried (Na₂SO₄), and evaporated, and the residue was distilled under reduced pressure to provide a colorless liquid (10.03 g, 92%). B.p.: 95–100 $^{\circ}\text{C}$ /15 mm Hg; IR (neat): $\tilde{\nu}$ = 1566, 1452, 1416, 1282, 1242, 1026, 833 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 0.27 (s, 9H), 3.93 (s, 3H), 6.62 (d, J = 8.2 Hz, 1H), 7.06 (d, J = 6.6 Hz, 1H), 7.45 (dd, J = 8.2, 6.6 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = -1.8, 53.1, 110.2, 122.3, 136.8, 163.5, 165.4; HRMS (EI): m/z calcd for C₉H₁₅NOSi (*M*⁺) 181.0923, found 181.0929; LRMS (EI): m/z = 181 (*M*⁺, 6), 166 (16), 150 (6).

4-Iodo-2-methoxy-6-trimethylsilyl-3-pyridinecarboxaldehyde (17): 1.7 N *n*BuLi in pentane (31 mL, 52.5 mmol) was added to a solution of **15** (9.07 g, 50 mmol) in THF (150 mL) at -78°C . After 1 h, *N,N,N'*-trimethyl-*N'*-formylethylenediamine (6.83 g, 52.5 mmol) was slowly added. The reaction was allowed to warm to -40°C , 1.6 N *n*BuLi in hexanes (63 mL, 100 mmol) was injected, and the mixture was stirred for 3 h at -30°C . A solution of I₂ (30.5 g, 120 mmol) in THF (200 mL) was then quickly added at -78°C with vigorous stirring. The resulting mixture was allowed to warm slowly to 0 $^{\circ}\text{C}$ (1 h), poured into 5% Na₂SO₃ (500 mL), and extracted with Et₂O (3 \times 300 mL). The combined organic layers were washed with 50% brine and with brine, dried (Na₂SO₄), and the residue obtained after removal of the solvents was subjected to flash chromatography (hexanes/AcOEt 95:5) to provide a yellow oil (8.20 g, 49%). IR (neat): $\tilde{\nu}$ = 1684, 1530, 1505, 1437, 1401, 1321, 1239, 1011, 828 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 0.27 (s, 9H), 4.03 (s, 3H), 7.66 (s, 1H), 10.17 (s, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = -2.1, 54.0, 108.4, 118.0, 135.5, 173.0, 191.1; HRMS (EI): m/z calcd for C₁₀H₁₄INO₂Si (*M*⁺) 334.9839, found 334.9833; LRMS (EI): m/z = 335 (*M*⁺, 60), 320 (100), 306 (13), 292 (20).

3-Crotyloxymethyl-4-iodo-2-methoxy-6-trimethylsilylpyridine (18): Crotyl alcohol (4.30 mL, 50 mmol), triethylsilane (4.80 mL, 30 mmol), and TFA (7.70 mL, 100 mmol) were successively added to a solution of pyridinecarboxaldehyde **17** (5.05 g, 15.0 mmol) in CH₂Cl₂ (15 mL) at 0 $^{\circ}\text{C}$. After 10 h at room temperature, the reaction mixture was slowly poured into saturated NaHCO₃ and the organic layer was washed with brine and dried (Na₂SO₄). The residue obtained after evaporation of the solvent was purified by flash chromatography (hexanes/AcOEt 95:5) to afford a slightly yellow oil (3.71 g, 63%). IR (neat): $\tilde{\nu}$ = 2942, 1551, 1520, 1446, 1333, 1240, 1084, 1022, 837, 750 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 0.24 (s, 9H), 1.69 (dd, J = 6.1, 1.0 Hz, 3H), 3.85–4.05 (m, 2H), 3.93 (s, 3H), 4.55 (s, 2H), 5.55–5.83 (m, 2H), 7.47 (s, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = -2.0, 17.9, 53.8, 69.7, 71.7, 114.0, 127.8, 129.8, 133.2, 161.5; HRMS (EI): m/z calcd for C₁₃H₁₉INO₂Si [*M* - CH₃]⁺ 376.0230, found 376.0239; LRMS (EI): m/z = 335 (56), 320 (100), 292 (38).

4-Ethyl-8-methoxy-6-trimethylsilyl-1H-3-pyreno[3,4-c]pyridine (19): A mixture of pyridine **18** (3.44 g, 8.80 mmol), tetrabutylammonium bromide (2.84 g, 8.80 mmol), anhydrous K₂CO₃ (2.44 g, 17.60 mmol), and Pd(OAc)₂ (200 mg, 0.88 mmol) in DMF (500 mL) was stirred at 85 $^{\circ}\text{C}$ for 18 h. The final solution was diluted with Et₂O (600 mL), filtered through a pad of Celite, washed with H₂O (4 \times 300 mL), and dried (Na₂SO₄). After concentration under reduced pressure, the crude product was subjected to flash chromatography (hexanes/AcOEt 95:5) to provide a colorless oil

(1.59 g 69%). IR (neat): $\tilde{\nu}$ = 2944, 1620, 1570, 1534, 1443, 1333, 1237, 1146, 1109, 858, 829 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 0.26 (s, 9H), 1.12 (t, J = 7.3 Hz, 3H), 2.31 (dq, J = 7.3, 1.0 Hz, 2H), 3.94 (s, 3H), 5.00 (s, 2H), 6.51 (t, J = 1.0 Hz, 1H), 6.83 (s, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = -1.8, 13.6, 20.8, 53.1, 62.7, 108.4, 114.5, 115.9, 139.0, 145.0, 158.7, 164.5; HRMS (EI): m/z calcd for C₁₄H₂₁NO₂Si (*M*⁺) 263.1342, found 263.1342; LRMS (EI): m/z = 263 (*M*⁺, 40), 248 (100), 217 (21), 189 (16), 166 (11).

(S)-4-Ethyl-4-hydroxy-8-methoxy-3-oxo-6-trimethylsilyl-1H-pyrano[3,4-c]-pyridine (20): Enol ether **19** (4.28 g, 16.3 mmol) was added to a vigorously stirred solution of K₂Fe(CN)₆ (16.3 g, 49.5 mmol), K₂CO₃ (6.86 g, 49.5 mmol), CH₃SO₂NH₂ (3.1 g, 31.7 mmol), (DHQD)₂-PYR (0.36 g, 0.41 mmol, 2.5 mol%), and OsO₄ (0.10 mL of a 2.5 w% in *t*BuOH, 0.50 mol%) in 1:1 *t*BuOH/H₂O (160 mL) at 0 $^{\circ}\text{C}$. The reaction mixture was stirred for 12 h and Na₂SO₃ (16.0 g) was slowly added. After 30 min, CH₂Cl₂ (100 mL) and H₂O (100 mL) were added, and the aqueous layer was further extracted with CH₂Cl₂ (50 mL). The combined organic layers were dried (Na₂SO₄) and concentrated, and the residue was subjected to flash chromatography (CH₂Cl₂/AcOEt 5:1) to give the product, an α -hydroxylactol, as a white solid. This solid was dissolved in MeOH/H₂O 10:1 (300 mL), and crystalline iodine (37.1 g, 0.15 mol, 9 equiv) and CaCO₃ (3.30 g, 32.5 mol, 2 equiv) were added. The reaction mixture was stirred for 32 h at room temperature. Et₂O (300 mL), H₂O (300 mL), and Na₂SO₃ (20 g) were then successively added. The organic layer was separated and dried (Na₂SO₄). Flash chromatography (hexanes/AcOEt 5:1) afforded α -hydroxylactone **20** as an oil (4.1 g 85%), 94% *ee* by NMR shift experiment [Eu(hfc)₃]. [α]_D²⁰ = +78.3 (c = 0.367, CH₂Cl₂); IR (neat): $\tilde{\nu}$ = 3536, 1738, 1585, 1455, 1352, 1249, 1227, 1159, 1106, 1035, 842 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 0.29 (s, 9H), 0.96 (t, J = 7.4 Hz, 3H), 1.79 (q, J = 7.4 Hz, 2H), 3.65 (s, 1H), 4.00 (s, 3H), 5.25 (d, J = 15.6 Hz, 1H), 5.56 (d, J = 15.6 Hz, 1H), 7.35 (s, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = -1.9, 7.8, 31.9, 53.4, 66.0, 73.0, 110.5, 118.0, 146.1, 150.0, 166.5, 174.6; HRMS (EI): m/z calcd for C₁₄H₂₁NO₄Si (*M*⁺) 295.1240, found 295.1237; LRMS (EI): m/z = 295 (*M*⁺, 24), 280 (55), 267 (20), 236 (26), 178 (14).

(S)-4-Ethyl-4-hydroxy-6-iodo-8-methoxy-3-oxo-1H-pyrano[3,4-c]pyridine (21): A solution of ICl (3.24 g, 20.0 mmol) in anhydrous CCl₄ (14 mL) was added to the hydroxylactone **20** (1.48 g, 5.00 mmol) in CH₂Cl₂ (20 mL) at 0 $^{\circ}\text{C}$, then the reaction mixture was stirred in the dark for 48 h at room temperature. The final solution was poured with vigorous stirring into an ice-cold 5% Na₂SO₃/brine 1:1 solution (300 mL). The resulting mixture was extracted with AcOEt (3 \times 150 mL). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure, and the residue was subjected to flash chromatography (hexanes/AcOEt 85:15) to afford, in order of elution, first the starting material **20** (0.70 g, 47%), then the iodo-derivative **21** (0.79 g, 45%) as an oil. [α]_D²⁰ = +34.0 (c = 1, CHCl₃); IR (neat): $\tilde{\nu}$ = 3449, 1730, 1572, 1447, 1356, 1225, 1149, 1088, 1030, 868, 752 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 0.93 (t, J = 7.3 Hz, 3H), 1.72 (q, J = 7.3 Hz, 2H), 3.65 (br s, 1H), 3.94 (s, 3H), 5.15 (d, J = 15.6 Hz, 1H), 5.46 (d, J = 15.6 Hz, 1H), 7.58 (s, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 7.7, 31.6, 54.8, 65.4, 72.8, 110.6, 113.5, 124.0, 149.5, 157.9, 173.7; HRMS (EI): m/z calcd for C₁₁H₁₂INO₄ (*M*⁺) 348.9811, found 348.9819; LRMS (EI): m/z = 349 (*M*⁺, 100), 320 (58), 305 (100), 276 (86), 178 (45).

(S)-4-Ethyl-4-hydroxy-6-iodo-3-oxo-1H-pyrano[3,4-c]-8-pyridone (22):

i) *Cleavage with TMSI:* Chlorotrimethylsilane (0.45 mL, 3.45 mmol) was slowly added to a solution of iodopyridine **21** (0.75 g, 2.15 mmol) and NaI (0.52 g, 3.45 mmol) in CH₃CN (7 mL), followed by water (19 μ L, 1.05 mmol). The mixture was heated in the dark at 65 $^{\circ}\text{C}$ for 5 h, poured into 5% Na₂SO₃/brine 1:1 (50 mL) and quickly extracted with AcOEt (4 \times 50 mL). After drying (Na₂SO₄) and removal of the solvents, the residue was purified by flash chromatography (CHCl₃/MeOH 9:1) and recrystallized (CHCl₃/MeOH) to provide a white solid (525 mg, 73%). [α]_D²⁰ = +49.9 (c = 1, MeOH); IR (neat): $\tilde{\nu}$ = 3532, 2984, 1748, 1594, 1461, 1380, 1162, 1100, 1054, 873 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 0.95 (t, J = 7.3 Hz, 3H), 1.77 (m, 2H), 4.12 (br s, 1H), 5.14 (d, J = 15.4 Hz, 1H), 5.55 (d, J = 15.4 Hz, 1H), 7.06 (s, 1H); ¹³C NMR (75 MHz, CDCl₃/CD₃OD 4:1): δ = 7.2, 31.0, 65.3, 72.0, 95.1, 115.3, 117.3, 150.7, 160.4, 173.2; HRMS (EI): m/z calcd for C₁₀H₁₀INO₄ (*M*⁺) 334.9655, found 334.9656; LRMS (EI): m/z = 335 (*M*⁺, 57), 306 (24), 291 (100), 262 (66), 234 (44).

ii) *Cleavage with HI:* 47% HI (3.50 mL, 21.4 mmol) was added to a solution of **21** (2.49 g, 7.13 mmol) in AcOEt (10 mL) and the reaction mixture was stirred overnight in the dark at room temperature. The final solution was slowly poured into ice-cold saturated NaHCO₃ (100 mL),

diluted with brine (100 mL), and extracted with AcOEt (8 × 50 mL). After drying (Na₂SO₄) and removal of the solvent, the residue was purified as above to give of **22**, (1.71 g, 72%).

General procedure for the N-alkylation of substituted 2-pyridones; (S)-4-ethyl-4-hydroxy-6-iodo-3-oxo-7-propargyl-1H-pyrano[3,4-c]-8-pyridone

(23): 60% NaH in mineral oil (43 mg, 1.06 mmol) was added to a solution of iodopyridone **22** (322 mg, 0.96 mmol) in DME (3.0 mL) and DMF (1.0 mL) at 0 °C under argon. LiBr (165 mg, 1.92 mmol) was added 10 min later. After 15 min at room temperature, 80% propargyl bromide in toluene (0.36 mL, 2.88 mmol) was injected and the reaction mixture was heated in the dark at 70 °C for 20 h. The final solution was poured into brine (20 mL), extracted with AcOEt (6 × 15 mL), and dried (Na₂SO₄). The residue obtained after removal of the solvents was subjected to flash chromatography (CHCl₃/AcOEt 85:15) to give a foam (280 mg, 78%). [α]_D²⁰ = +59.1 (*c* = 1, CHCl₃); IR (neat): $\tilde{\nu}$ = 3381, 3278, 1738, 1644, 1595, 1527, 1225, 1134, 1041, 752 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 0.95 (t, *J* = 7.3 Hz, 3H), 1.75 (m, 2H), 2.35 (t, *J* = 2.5 Hz, 1H), 3.69 (brs, 1H), 5.07 (brs, 2H), 5.10 (d, *J* = 16.4 Hz, 1H), 5.48 (d, *J* = 16.4 Hz, 1H), 7.17 (s, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 7.8, 31.6, 44.0, 66.2, 71.9, 73.6, 100.2, 116.8, 118.3, 148.9, 158.2, 173.2; HRMS (EI): *m/z* calcd for C₁₃H₁₂INO₄ (*M*⁺) 372.9811, found 372.9809; LRMS (EI): *m/z* = 373 (*M*⁺, 100), 344 (27), 329 (25), 217 (17).

General procedure for the radical cascade reaction between aryl isonitriles and 6-iodo-2-pyridones; (20S)-camptothecin (1a): i) *From the propargyl precursor*: A solution of **23** (37.3 mg, 0.10 mmol), phenyl isonitrile (0.30 mmol), and hexamethylditin (51 mg, 0.15 mmol) in benzene (1.5 mL) under Ar was irradiated at 70 °C with a 275 W GE sunlamp for 5 h without stirring; every 30 min the vessel was tapped to allow the solid sticking on the walls to drop to the bottom of the flask where it was protected from further irradiation by aluminum foil. After cooling, the solid was filtered, rinsed with Et₂O (2 mL) [Note: this procedure was used for **1a**; in the case of most other derivatives, the final solution was diluted with CHCl₃/MeOH and concentrated], and subjected to flash chromatography (CHCl₃/CH₃CN/MeOH 90:5:5) to give **1a** (21.8 mg, 63%). [α]_D²⁰ = +39.9 (*c* = 0.2, CHCl₃/MeOH 4:1) [ref. [16] +42.0, (*c* = 0.51, CHCl₃/MeOH 4:1)].

ii) *From the allyl precursor*: In a similar manner **25d** (40.1 mg, 0.11 mmol) provided **1a** (7.7 mg, 21%).

Preparation of aryl isonitriles:

1. 1,4'-Bipiperidinyl-1'-carboxylic acid, 4-isocyanophenylester 24:

1,4'-Bipiperidinyl-1'-carboxylic acid, 4-nitrophenyl ester: Triethylamine (10.7 mL, 76.2 mmol) was added to a solution of 4-nitrophenyl chloroformate (5.15 g, 25.6 mmol) in dry THF (150 mL) at -78 °C. Next a solution of 4-piperidinopiperidine (4.51 g, 25.6 mmol) in THF (40 mL) was added. After 2 h, the solvent was removed and the residue was taken up in AcOEt, filtered, and evaporated. The crude yellow solid was passed through a pad of neutral alumina with AcOEt to yield, after evaporation, a white solid (6.73 g, 79%). IR (CHCl₃): $\tilde{\nu}$ = 3046, 2937, 2859, 1704, 1620, 1513, 1466, 1242, 1197 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 1.20–1.80 (m, 8H), 1.90 (d, *J* = 12.7 Hz, 2H), 2.20–2.70 (m, 5H), 2.87 (t, *J* = 12 Hz, 1H), 3.01 (t, *J* = 12 Hz, 1H), 4.30 (brs, 2H), 7.29 (d, *J* = 9 Hz, 2H), 8.26 (d, *J* = 9 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃): δ = 24.6, 26.3, 27.5, 28.2, 40.1, 44.4, 50.1, 62.0, 122.2, 124.9, 144.8, 151.9, 156.3; HRMS (EI): *m/z* calcd for C₁₇H₂₃N₃O₄ (*M*⁺) 333.1676, found 333.1688; LRMS (EI): *m/z* = 333 (*M*⁺), 195, 167, 124, 110, 96, 55.

1,4'-Bipiperidinyl-1'-carboxylic acid, 4-aminophenyl ester: The above carbamate (1.01 g, 3.03 mmol) was dissolved in AcOEt (125 mL) and 10% Pd/C (0.150 g) was added. A balloon of H₂ was attached and the mixture was stirred for 12 h. The catalyst was removed by filtration through Celite and the solvent was evaporated to give a white solid (835 mg, 91%). IR (CHCl₃): $\tilde{\nu}$ = 3453, 3400, 3028, 2936, 2859, 1703, 1513, 1429, 1242, 1226, 1210, 1197 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 1.30–1.70 (m, 8H), 1.86 (d, *J* = 12.6 Hz, 2H), 2.33–2.62 (m, 5H), 2.68–3.04 (m, 2H), 3.58 (brs, 2H), 4.30 (brs, 2H), 6.64 (d, *J* = 6 Hz, 2H), 6.87 (d, *J* = 6 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃): δ = 24.6, 26.3, 27.5, 28.1, 43.8, 43.9, 50.1, 62.3, 115.4, 122.3, 143.4, 143.7, 154.1; HRMS (EI): *m/z* calcd for C₁₇H₂₃N₃O₂ (*M*⁺) 303.1944, found 303.1947; LRMS (EI): *m/z* = 303 (*M*⁺), 195, 167, 124, 108, 96, 80, 65, 55.

1,4'-Bipiperidinyl-1'-carboxylic acid, 4-formylaminophenyl ester: Formic acid 98% (60.7 mg, 1.32 mmol) was added to a flask containing DCC

(272 mg, 1.32 mmol) and CH₂Cl₂ (5 mL) at 0 °C. The resulting solution was transferred to a round-bottom flask containing the above amine (200 mg, 0.66 mmol) and pyridine (5 mL). After 3 h the pyridine was evaporated and the residue was taken up in CH₂Cl₂, filtered, evaporated, and applied directly to a basic alumina column (CH₂Cl₂/MeOH 95:5) to give a white solid (118 mg, 83%). IR (CHCl₃): $\tilde{\nu}$ = 3025, 3013, 2937, 2888, 2861, 1703, 1517, 1466, 1275, 1226, 1210 cm⁻¹; ¹H NMR (300 MHz, CDCl₃ mixture of rotamers): δ = 1.38–1.80 (m, 8H), 1.90 (d, *J* = 12 Hz, 2H), 2.40–2.70 (m, 5H), 2.83 (t, *J* = 12 Hz, 1H), 2.97 (t, *J* = 12 Hz, 1H), 4.32 (m, 2H), 7.028–7.11 (m, 3H), 7.37 (brs, 0.5H, *cis*), 7.46 (d, *J* = 10 Hz, 1H), 7.53 (d, *J* = 11 Hz, 0.5H), 8.32 (d, *J* = 2 Hz, 0.5H), 8.59 (d, *J* = 11 Hz, 0.5H); ¹³C NMR (75 MHz, CDCl₃): δ = 24.6, 26.3, 27.6, 28.1, 44.2, 44.0, 50.1, 82.2, 120.0, 121.0, 122.1, 123.0, 133.9, 134.3, 147.5, 148.9, 153.9, 153.4, 159.1, 162.5; HRMS (EI): *m/z* calcd for C₁₈H₂₅N₃O₃ (*M*⁺) 331.1884, found 331.1896; LRMS (EI): *m/z* = 331 (*M*⁺), 244, 202, 167, 124, 80, 55.

1,4'-Bipiperidinyl-1'-carboxylic acid, 4-isocyanophenylester (24): A solution of triphosgene (68 mg, 0.230 mmol) in CH₂Cl₂ (10 mL) was added dropwise to a flask containing the above formamide (90.1 mg, 0.272 mmol), triethylamine (69.5 mg, 0.688 mmol), and CH₂Cl₂ (10 mL) at 0 °C. After 2 h at 22 °C, the reaction was extracted with ether (30 mL) and 7% NaHCO₃ (5 mL). The organic layer was dried with MgSO₄, filtered, and evaporated. The crude brown residue was subjected to flash chromatography on silica gel (Et₂O/Et₂NH 95:5) to give an off-white solid (67.2 mg, 79%). IR (CHCl₃): $\tilde{\nu}$ = 3034, 2937, 2131, 1718, 1504, 1429, 1233, 1224, 1213, 1198, 1184 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 1.32–1.75 (m, 8H), 1.90 (brd, *J* = 12.4 Hz, 2H), 2.32–2.65 (m, 5H), 2.84 (t, *J* = 12.3 Hz, 1H), 2.98 (t, *J* = 12.1 Hz, 1H), 4.20–4.40 (m, 2H), 7.14 (d, *J* = 8.8 Hz, 2H), 7.37 (d, *J* = 8.8 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃): δ = 25.0, 26.5, 27.8, 28.5, 44.4, 50.6, 62.7, 123.3, 127.8, 152.1, 153.1, 164.4; HRMS (EI): *m/z* calcd for C₁₈H₂₃N₃O₂ (*M*⁺) 313.1779, found 313.1790; LRMS (EI): *m/z* = 313 (*M*⁺), 195, 167, 124, 110, 84, 55.

2. 4-Acetoxyphenyl isonitrile (24b): Tetrabromomethane (730 mg, 2.20 mmol), triphenylphosphine (575 mg, 2.20 mmol), and triethylamine (310 μ L, 2.20 mmol) were successively added to a solution of 4-acetoxyformanilide (358 mg, 2.00 mmol) in CH₂Cl₂ (10 mL) at 0 °C, and the resulting mixture was refluxed in the dark for 3 h. After evaporation of the solvents, the crude mixture was triturated in ice-cold Et₂O (10 mL) and filtered. The solvent was evaporated and the residue was purified by flash chromatography (hexanes/AcOEt 8:2) to provide a brownish foam (243 mg, 76%). IR (neat): $\tilde{\nu}$ = 2127, 1768, 1501, 1370, 1201, 1180, 909 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 2.29 (s, 3H), 7.11 (d, *J* = 8.8 Hz, 2H), 7.38 (d, *J* = 8.8 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃): δ = 21.0, 122.8, 127.6, 150.8, 164.3, 168.8; HRMS (EI): *m/z* calcd for C₉H₇NO₂ (*M*⁺) 161.0477, found 161.0474; LRMS (EI): *m/z* = 161 (*M*⁺, 14), 133 (10), 119 (100), 91 (9).

3. 4-tert-Butyloxycarbonylaminophenyl isonitrile (24c): Boc-protection of 4-aminofornanilide (1.71 g, 12.6 mmol) under the conditions of Luche^[46], after 3 h and flash chromatography (CHCl₃/MeOH 95:5) gave 2.85 g (96%) of *tert*-butyloxycarbonylaminofornanilide, as a white solid. As for **24b**, dehydration of this solid (945 mg, 4.0 mmol) followed by flash chromatography (hexanes/AcOEt 9:1), provided **24c** as a brownish solid (502 mg, 58%). M.p.: 128–129 °C; IR (NaCl): $\tilde{\nu}$ = 3370, 2121, 1691, 1524, 1412, 1364, 1239, 1158, 832 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 1.48 (s, 9H), 6.75 (brs, 1H), 7.26 (d, *J* = 8.8 Hz, 2H), 7.37 (d, *J* = 8.8 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃): δ = 28.2, 81.3, 118.5, 127.1, 139.4, 152.3, 162.7; HRMS (EI): *m/z* calcd for C₁₂H₁₄N₂O₂ (*M*⁺) 218.1055, found 218.1044; LRMS (EI): *m/z* = 218 (*M*⁺, 30), 162 (72), 144 (100).

4. 3-(1-tert-Butyldiphenylsilyloxyethyl)phenyl isonitrile (28): *N*-Formylation^[35] of 3-(1-hydroxyethyl)aniline (**26**), followed by standard TBDPS-protection^[35] provided *N*-3-(1-tert-butylidiphenylsilyloxyethyl)formanilide (**27**) in 100% yield as an oil. As for **24b**, dehydration of **27** (4.23 g, 10.5 mmol) followed by flash chromatography (hexanes/CH₂Cl₂ 8:2) provided **28** as a colorless oil (2.38 g, 59%). IR (neat): $\tilde{\nu}$ = 2126, 1428, 1111, 702 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 1.04 (s, 9H), 1.30 (d, *J* = 6.4 Hz, 3H), 4.77 (q, *J* = 6.4 Hz, 1H), 7.15–7.28 (m, 6H), 7.32–7.50 (m, 6H), 7.65–7.70 (m, 2H); ¹³C NMR (75 MHz, CDCl₃): δ = 26.7, 26.9, 71.1, 123.5, 124.6, 126.3, 127.6, 129.1, 129.8, 133.2, 133.8, 135.8; HRMS (EI): *m/z* calcd for C₂₁H₁₈NOSi [*M* - *t*-Bu⁺] 328.1158, found 328.1149; LRMS (EI): *m/z* = 328 [*M* - *t*-Bu⁺], 36), 199 (100), 77 (18).

5. 3-tert-Butyloxycarbonylaminophenyl isonitrile (31): Boc-protection of 3-aminoformanilide (1.80 g, 13.2 mmol) under the conditions of Luche^[46]

after 3 h and flash chromatography (CHCl₃/MeOH 95:5), gave 2.65 g (85%) of 3-*tert*-butyloxycarbonylaminoformanilide as a white solid. As for **24b**, dehydration of this solid (412 mg, 1.74 mmol) followed by flash chromatography (hexanes/AcOEt 9:1) provided **31** as a brown solid (190 mg, 50%). M.p.: 95–97 °C; IR (NaCl): $\tilde{\nu}$ = 3318, 2126, 1715, 1603, 1547, 1433, 1236, 1162, 782 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 1.49 (s, 9H), 6.67 (brs, 1H), 7.00 (m, 1H), 7.20–7.30 (m, 2H), 7.60 (brs, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 28.2, 81.3, 116.0, 118.9, 120.6, 129.8, 139.5, 152.3, 163.6; HRMS (EI): m/z calcd for C₁₂H₁₄N₂O₂ (M⁺) 218.1055, found 218.1047; LRMS (EI): m/z = 218 (M⁺, 25), 196 (41), 162 (50), 152 (83), 118 (100).

6. 3-Methyl-6-trimethylsilylphenyl isonitrile (35):

3-Methyl-1-nitro-6-trimethylsilylbenzene (33): A solution of 4-chloro-3-nitrotoluene (**32**) (2.58 g, 15 mmol), hexamethyldisilane (6.2 mL, 30 mmol) and tetrakis(triphenylphosphine)palladium (260 mg, 0.22 mmol) in xylene (75 mL) was stirred in the dark in a sealed tube at 150 °C for 40 h. Hexanes (60 mL) was added, the solution was filtered over Celite, and the solvents were removed by distillation. The resulting crude product was purified by flash chromatography (hexanes/AcOEt 95:5) to provide a yellow oil (2.00 g, 64%). IR (neat): $\tilde{\nu}$ = 1516, 1341, 1240, 1109, 839, 746 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 0.31 (s, 9H), 2.43 (s, 3H), 7.41 (brd, J = 7.3 Hz, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.98 (brs, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = -0.4, 20.9, 124.5, 132.9, 134.0, 136.1, 140.7, 153.7; HRMS (EI): m/z calcd for C₉H₁₂NO₂Si [M - CH₃⁺] 194.0637, found 194.0637; LRMS (EI): m/z = 194 [M - CH₃⁺], 24, 164 (100), 149 (56), 105 (19).

6-Trimethylsilyl-*m*-toluidine (34): Reduction of **33** (620 mg, 3.0 mmol) under the conditions of Ehrenkauf^[38] gave a slightly yellow oil (575 mg, 97%). IR (neat): $\tilde{\nu}$ = 3365, 1551, 1404, 1293, 1244, 835, 758 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 0.37 (s, 9H), 2.30 (s, 3H), 3.76 (brs, 2H), 6.51 (s, 1H), 6.65 (d, J = 8.0 Hz, 1H), 7.24 (d, J = 7.5 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = -0.6, 21.3, 116.1, 119.4, 135.1, 140.7, 151.5; HRMS (EI): m/z calcd for C₁₀H₁₇NSi (M⁺) 179.1130, found 179.1130; LRMS (EI): m/z = 179 (M⁺, 29), 164 (100), 147 (53), 105 (19).

3-Methyl-6-trimethylsilylphenyl isonitrile (35): Formic acid (0.57 mL, 15 mmol) was added to a solution of DCC (3.09 g, 15 mmol) in CH₂Cl₂ (20 mL) at 0 °C and the mixture was vigorously stirred for 5 min. A solution of **34** (0.90 g, 5 mmol) in CH₂Cl₂ (5 mL) and pyridine (2.5 mL) was slowly added and the reaction mixture was stirred for 1 h at 0 °C. The final solution was diluted with Et₂O (50 mL), filtered, and washed successively with H₂O, 1N HCl (3 × 20 mL), and brine. After drying (Na₂SO₄) and evaporation of the solvents, the residue was subjected to flash chromatography (CHCl₃/AcOEt 8:2) to afford 0.94 g (90%) of a white solid. As for **24b**, dehydration of this solid (0.83 g, 4.0 mmol) followed by flash chromatography (hexanes/AcOEt 96:4), provided **35** as a colorless oil (0.68 g, 89%). IR (neat): $\tilde{\nu}$ = 2097, 1590, 1437, 1240, 1129, 1057, 914, 837, 758 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 0.39 (s, 9H), 2.33 (s, 3H), 7.12–7.20 (m, 2H), 7.37 (d, J = 8.1 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = -1.6, 20.9, 127.8, 129.5, 133.2, 134.7, 140.4, 164.8; HRMS (EI): m/z calcd for C₁₁H₁₅NSi (M⁺) 189.0974, found 189.0974; LRMS (EI): m/z = 189 (M⁺, 17), 174 (100), 105 (10).

7. 3-Fluoro-2-trimethylsilylphenyl isonitrile (39a) and 3,4-methylenedioxy-2-trimethylsilylphenyl isonitrile (39b):

3-Fluoro-2-trimethylsilylbenzaldehyde (37a): 1.6N *n*BuLi in hexanes (13 mL, 21 mmol) was slowly added to a solution of *N,N,N'*-trimethylethylenediamine (2.70 mL, 20 mmol) in THF (50 mL) at -20 °C, followed by 3-fluorobenzaldehyde (**36a**) (2.10 mL, 20 mmol) 15 min later. After 15 min at -20 °C, 1.6N *n*BuLi in hexanes (38 mL, 60 mmol) was injected and the solution was stirred for 1.5 h at -35 °C. Chlorotrimethylsilane (15 mL, 120 mmol) was added and the reaction mixture was stirred overnight at room temperature. The final solution was poured into ice-cold 1N HCl (150 mL), quickly extracted with Et₂O (3 × 100 mL), washed with brine, and dried (Na₂SO₄). After evaporation of the solvents, the residue was purified by flash chromatography (hexanes/AcOEt 95:5) to give a yellow oil (3.25 g, 83%). IR (neat): $\tilde{\nu}$ = 1701, 1440, 1252, 1233, 1109, 848, 764 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 0.40 (d, J = 2.6 Hz, 9H), 7.18 (brt, J = 9.0 Hz, 1H), 7.47 (ddd, $J_1 = J_2 = 8.1$ Hz, $J_3 = 5.4$ Hz, 1H), 7.70 (brd, J = 7.5 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 1.8, 120.8 (d, $J_{CF} = 29$ Hz), 126.8, 128.2, 131.2, 143.3, 167.6 (d, $J_{CF} = 244$ Hz), 192.4; HRMS (EI): m/z calcd for C₉H₁₀FOSi [M - CH₃⁺] 181.0485, found 181.0482; LRMS (EI): m/z = 181 [M - CH₃⁺], 100, 151 (6), 125 (13), 103 (9), 91 (33).

2-Trimethylsilylpiperonal (37b): Use of the procedure described for the synthesis of **37a** and stirring the dianion at -20 °C for 3 h, piperonal (**36b**) (3.00 g, 20 mmol) gave a yellow oil (2.25 g, 51%) after flash chromatography (hexanes/AcOEt 95:5). IR (neat): $\tilde{\nu}$ = 1688, 1570, 1422, 1246, 1213, 1058, 843 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 0.31 (s, 9H), 5.93 (s, 2H), 6.82 (d, J = 8.1 Hz, 1H), 7.38 (d, J = 8.1 Hz, 1H), 9.81 (s, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 1.4, 100.1, 108.4, 119.8, 131.0, 136.0, 151.1, 154.1, 191.4; HRMS (EI): m/z calcd for C₁₀H₁₁O₃Si [M - CH₃⁺] 207.0477, found 207.0496; LRMS (EI): m/z = 222 (M⁺, 2), 207 (100), 177 (11), 149 (11).

3-Fluoro-2-trimethylsilylphenyl isocyanate (38a): A solution of 80% NaClO₂ (2.55 g, 22.6 mmol) and NaH₂PO₄ · H₂O (3.10 g, 22.6 mmol) in H₂O (18 mL) was slowly added to a solution of **37a** (3.41 g, 17.3 mmol) and 2-methyl-2-butene (12 mL) in *tert*-butanol (20 mL) over a period of 10 min. After 16 h at room temperature, *tert*-butanol was evaporated and the mixture was poured into 1N NaOH (50 mL). The aqueous layer was washed with hexanes (3 × 15 mL), acidified with 1N HCl to pH 2, saturated with brine (50 mL), and extracted with Et₂O (3 × 50 mL). After drying (Na₂SO₄) and evaporation of the solvents, 3-fluoro-2-trimethylsilylbenzoic acid was obtained (3.13 g, 85%), as a white solid. M.p.: 65–67 °C; IR (NaCl): $\tilde{\nu}$ = 2982, 1700, 1434, 1294, 1271, 1253, 1230, 849, 763 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 0.39 (d, J = 2.6 Hz, 9H), 7.16 (brt, J = 9.1 Hz, 1H), 7.41 (ddd, $J_1 = J_2 = 7.9$ Hz, $J_3 = 5.6$ Hz, 1H), 7.73 (brd, J = 7.7 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 1.3, 119.5 (d, $J_{CF} = 27$ Hz), 126.0, 127.3, 130.9, 138.0, 167.5 (d, $J_{CF} = 243$ Hz), 174.5; HRMS (EI): m/z calcd for C₉H₁₀FO₂Si [M - CH₃⁺] 197.0434, found 197.0433; LRMS (EI): m/z = 197 [M - CH₃⁺], 100, 179 (10), 133 (9), 115 (14), 105 (15). Oxalyl chloride (1.30 mL, 15.0 mmol) was added to a solution of this acid (3.03 g, 14.3 mmol) in CH₂Cl₂ (20 mL) and the resulting mixture was stirred for 3 h at room temperature. The residue obtained after evaporation of the solvent was diluted with THF (5 mL) and injected with vigorous stirring into an ice-cold solution of NaN₃ (3.70 g, 57 mmol) in H₂O (20 mL) and acetone (50 mL). After 15 min at 0 °C and 1 h at room temperature, the solution was extracted with Et₂O (4 × 50 mL) and dried (Na₂SO₄). The residue obtained after evaporation of solvents was refluxed in toluene for 1 h to provide, upon solvent removal, **38a** as a slightly yellow oil (2.85 g, 79%). IR (neat): $\tilde{\nu}$ = 2269, 1598, 1433, 1252, 1228, 846, 788 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 0.38 (d, J = 1.9 Hz, 9H), 6.82 (brt, J = 8.3 Hz, 1H), 6.90 (brd, J = 8.2 Hz, 1H), 7.25 (ddd, $J_1 = J_2 = 8.1$ Hz, $J_3 = 6.6$ Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 0.4, 112.6 (d, $J_{CF} = 26$ Hz), 120.5, 122.5, 131.5, 139.2, 167.4 (d, $J_{CF} = 241$ Hz).

3,4-Methylenedioxy-2-trimethylsilylphenyl isocyanate (38b): This compound was prepared by means of the same sequence of reactions as for the preparation of **38a**. Oxidation of **37b** (1.72 g, 7.73 mmol) followed by flash chromatography (CHCl₃/AcOEt 9:1) gave 3,4-methylenedioxy-2-trimethylsilylbenzoic acid (1.60 g, 87%) as a white solid. M.p.: 152–154 °C; IR (NaCl): $\tilde{\nu}$ = 2976, 1686, 1576, 1422, 1279, 1243, 1147, 1054, 828, 764 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 0.37 (s, 9H), 5.97 (s, 2H), 6.82 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 1.7, 100.6, 108.1, 121.7, 127.4, 128.1, 150.3, 153.7, 173.7; HRMS (EI): m/z calcd for C₁₀H₁₁O₄Si [M - CH₃⁺] 223.0427, found 223.0425; LRMS (EI): m/z = 223 [M - CH₃⁺], 100, 207 (35), 193 (14), 165 (14). This solid (1.61 g, 6.76 mmol) was then converted to the acyl azide and subjected to the Curtius rearrangement to provide **38b** (1.63 g, 92%) as a colorless oil. IR (neat): $\tilde{\nu}$ = 2272, 1417, 1248, 1232, 1146, 1048, 886, 842 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 0.34 (s, 9H), 5.90 (s, 2H), 6.58 (d, J = 8.2 Hz, 1H), 6.70 (d, J = 8.2 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 0.0, 100.7, 109.2, 114.7, 119.5, 124.1, 144.1, 152.7; HRMS (EI): m/z calcd for C₁₁H₁₃NO₃Si (M⁺) 235.0665, found 235.0657; LRMS (EI): m/z = 235 (M⁺, 15), 221 (100), 190 (20).

3-Fluoro-2-trimethylsilylphenyl isonitrile (39a): Triethylamine (4.10 mL, 29.2 mmol) was added slowly to a solution of trichlorosilane (1.70 mL, 16.8 mmol) in CH₂Cl₂ (40 mL) followed 5 min later by **38a** (2.35 g, 11.2 mmol). After 1.5 h at 0 °C and 30 min at room temperature, the solution was saturated with gaseous NH₃, filtered over Celite, washed with 5% NaH₂PO₄ and dried (Na₂SO₄). The crude residue obtained after evaporation of the solvent was subjected to flash chromatography (hexanes/AcOEt 95:5) to give a slightly purple liquid (1.42 g, 66%). IR (neat): $\tilde{\nu}$ = 2114, 1598, 1440, 1254, 1237, 1110, 943, 848, 793 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 0.45 (d, J = 1.8 Hz, 9H), 7.01 (brt, J = 8.3 Hz, 1H), 7.17 (brd, J = 7.7 Hz, 1H), 7.32 (ddd, $J_1 = J_2 = 8.0$ Hz, $J_3 = 6.1$ Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 0.1, 116.5 (d, $J_{CF} = 26$ Hz), 124.3, 131.6, 166.8 (d, $J_{CF} = 243$ Hz), 166.9; HRMS (EI): m/z calcd for C₁₀H₁₂FNSi (M⁺)

193.0723, found 193.0715; LRMS (EI): $m/z = 193$ (M^+ , 30), 178 (100), 150 (39), 116 (33), 105 (41).

3,4-Methylenedioxy-2-trimethylsilylphenyl isonitrile (39b): Use of the procedure described for the synthesis of **39a** with **38b** (1.44 g, 6.12 mmol) provided a yellow solid (0.91 g, 68%) after flash chromatography (hexanes/AcOEt 9:1). M.p.: 81–82 °C; IR (NaCl): $\tilde{\nu} = 2115, 1431, 1247, 1150, 1057, 900, 845, 816, 772$ cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta = 0.40$ (s, 9H), 5.93 (s, 2H), 6.68 (d, $J = 8.1$ Hz, 1H), 6.86 (d, $J = 8.1$ Hz, 1H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3): $\delta = -0.4, 101.1, 108.8, 116.3, 122.4, 124.4, 146.8, 152.5, 183.9$; HRMS (EI): m/z calcd for $\text{C}_{11}\text{H}_{13}\text{NO}_2\text{Si}$ (M^+) 219.0716, found 219.0715; LRMS (EI): $m/z = 219$ (M^+ , 55), 204 (67), 174 (100).

Preparation of radical precursor iodopyridones **25a–f**:

1. (S)-4-Ethyl-4-hydroxy-6-iodo-3-oxo-7-(2-pentynyl)-1H-pyrano[3,4-c]-8-pyridone (25a): As for **23, 22** (100 mg, 0.30 mmol) and 2-pentynyl bromide (140 mg, 0.48 mmol) gave a slightly yellow oil (80 mg, 67%) after flash chromatography ($\text{CH}_2\text{Cl}_2/\text{AcOEt}$ 8:1). IR (neat): $\tilde{\nu} = 3429, 2978, 2937, 1748, 1645, 1531, 1140$ cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta = 0.93$ (t, $J = 7.4$ Hz, 3H), 1.09 (t, $J = 7.5$ Hz, 3H), 1.78 (m, 2H), 2.12 (m, 2H), 3.91 (s, 2H), 5.03 (m, 2H), 5.09 (d, $J = 16.3$ Hz, 1H), 5.46 (d, $J = 16.3$ Hz, 1H), 7.16 (s, 1H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3): $\delta = 7.7, 12.5, 13.4, 31.5, 44.5, 71.8, 72.3, 87.3, 100.4, 116.5, 118.2, 148.6, 173.2$; HRMS (EI): m/z calcd for $\text{C}_{15}\text{H}_{16}\text{INO}_4$ (M^+) 401.0124, found 401.0123; LRMS (EI): $m/z = 401$ (M^+ , 78), 366 (63), 342 (23), 108 (24).

2. (4S)-4-Ethyl-4-hydroxy-6-iodo-3-oxo-7-[5-(2-tetrahydropyranyloxy)-2-pentynyl]-1H-pyrano[3,4-c]-8-pyridone (mixture of tetrahydropyranyloxy isomers) (25b): As for **23, 22** (100 mg, 0.298 mmol) and 5-(2-tetrahydropyranyloxy)-2-pentynyl bromide (185 mg, 0.750 mmol) afforded a slightly yellow oil (67.1 mg, 45%) after flash chromatography ($\text{CHCl}_3/\text{AcOEt}$ 9:1). $[\alpha]_D^{20} = +36.2$ ($c = 1, \text{CHCl}_3$); $^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta = 0.93$ (t, $J = 7.3$ Hz, 3H), 1.40–1.90 (m, 6H), 2.48 (m, 2H), 3.40–3.60 (m, 2H), 3.65 (s, 1H), 3.70–3.90 (m, 2H), 4.60 (t, $J = 3.2$ Hz, 1H), 5.04 (brs, 2H), 5.09 (d, $J = 16.4$ Hz, 1H), 5.47 (d, $J = 16.4$ Hz, 1H), 7.15 (s, 1H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3): $\delta = 7.7, 19.3, 20.3, 25.3, 30.4, 31.5, 44.5, 62.1, 65.3, 66.3, 74.0, 82.8, 98.6, 100.3, 116.4, 118.1, 148.5, 173.1$; HRMS (EI): m/z calcd for $\text{C}_{20}\text{H}_{24}\text{INO}_6$ (M^+) 501.0648, found 501.0649; LRMS (EI): $m/z = 501$ (M^+ , 1), 472 (3), 428 (5), 417 (24), 401 (22), 386 (100).

3. (S)-4-Ethyl-4-hydroxy-6-iodo-3-oxo-7-(cyanomethyl)-1H-pyrano[3,4-c]-8-pyridone (25c): As for **23, 22** (60.0 mg, 0.179 mmol) and bromoacetonitrile (38 μL , 0.54 mmol) provided a slightly yellow oil (49.3 mg, 74%) after flash chromatography ($\text{CHCl}_3/\text{AcOEt}$ 6:4). $[\alpha]_D^{20} = +53.0$ ($c = 1, \text{CHCl}_3$); $^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta = 0.96$ (t, $J = 7.3$ Hz, 3H), 1.77 (m, 2H), 3.78 (brs, 1H), 5.10 (d, $J = 16.5$ Hz, 1H), 5.13 (d, $J = 17.0$ Hz, 1H), 5.27 (d, $J = 17.0$ Hz, 1H), 5.45 (d, $J = 16.5$ Hz, 1H), 7.22 (s, 1H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3): $\delta = 7.6, 31.5, 41.7, 65.8, 98.8, 113.5, 117.3, 118.5, 149.8, 157.7, 172.8$; HRMS (EI): m/z calcd for $\text{C}_{12}\text{H}_{11}\text{N}_3\text{IO}_4$ (M^+) 373.9764, found 373.9791; LRMS (EI): $m/z = 374$ (M^+ , 100), 345 (27), 330 (76), 290 (17), 203 (64), 191 (30), 163 (72).

4. (S)-4-Ethyl-4-hydroxy-6-iodo-3-oxo-7-allyl-1H-pyrano[3,4-c]-8-pyridone (25d): As for **23, 22** (50.0 mg, 0.149 mmol) and allylbromide (40 μL , 0.45 mmol) provided a slightly yellow oil (46.1 mg, 83%) after flash chromatography ($\text{CHCl}_3/\text{AcOEt}$ 90:10). $[\alpha]_D^{20} = +51.9$ ($c = 1, \text{CHCl}_3$); IR (neat): $\tilde{\nu} = 3366, 1732, 1634, 1518, 1422, 1221, 1148, 1039, 749$ cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta = 0.95$ (t, $J = 7.4$ Hz, 3H), 1.76 (m, 2H), 3.70 (s, 1H), 4.94 (m, 2H), 5.09 (d, $J = 16.3$ Hz, 1H), 5.18 (brd, $J = 16.7$ Hz, 1H), 5.29 (brd, $J = 10.4$ Hz, 1H), 5.47 (d, $J = 16.3$ Hz, 1H), 5.89 (dd, $J = 16.7, 10.4$ Hz, 1H), 7.15 (s, 1H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3): $\delta = 7.7, 31.5, 56.1, 66.3, 71.8, 101.2, 116.3, 118.1, 118.7, 130.5, 148.7, 158.2, 173.3$; HRMS (EI): m/z calcd for $\text{C}_{13}\text{H}_{14}\text{INO}_4$ (M^+) 374.9968, found 374.9951; LRMS (EI): $m/z = 375$ (M^+ , 100), 360 (68), 346 (15), 316 (16), 248 (23).

5. (S)-4-Ethyl-4-hydroxy-6-iodo-3-oxo-7-(4-chloro-2-butynyl)-1H-pyrano[3,4-c]-8-pyridone (25e): As for **23, 22** (250 mg, 0.75 mmol) and 1,4-dichloro-2-butyne (275 mg, 2.24 mmol) provided **25e** (200 mg, 63%) along with the *O*-alkylated product (42 mg, 13%) after flash chromatography ($\text{CH}_2\text{Cl}_2/\text{AcOEt}$ 8:2). IR (neat): $\tilde{\nu} = 3370, 2980, 1745, 1646, 1529, 1140$ cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta = 0.92$ (t, $J = 7.4$ Hz, 3H), 1.77 (m, 2H), 3.90 (s, 1H), 4.11 (t, $J = 1.8$ Hz, 2H), 5.10 (d, $J = 16.4$ Hz, 1H), 5.13 (t, $J = 1.8$ Hz, 2H), 5.46 (d, $J = 16.4$ Hz, 1H), 7.18 (s, 1H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3): $\delta = 7.7, 30.2, 31.6, 44.1, 66.2, 71.9, 79.6, 79.9, 100.0, 116.7, 118.3, 148.9, 158.0, 173.13$.

6. (S)-4-Ethyl-4-hydroxy-6-iodo-3-oxo-7-(4-methylpyrazinomethyl)-1H-pyrano[3,4-c]-8-pyridone (25f): A solution of **25e** (180 mg, 0.43 mmol), *N*-methylpiperazine (130 mg, 1.30 mmol), and *n*- Bu_4NI (16 mg, 0.043 mmol) in DME (3 mL) was stirred for 8 h. DME and excess *N*-methylpiperazine were removed and the residue was subjected to flash chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 5:1) to provide a colorless oil (185 mg, 89%). IR (neat): $\tilde{\nu} = 2911, 1732, 1644, 1636, 1520, 1449, 1439, 1414, 1130, 727$ cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta = 0.97$ (t, $J = 7.3$ Hz, 3H), 1.78 (m, 2H), 2.34 (s, 3H), 2.67 (brs, 4H), 3.31 (t, $J = 1.7$ Hz, 2H), 5.11 (d, $J = 16.4$ Hz, 1H), 5.12 (t, $J = 1.8$ Hz, 2H), 5.49 (d, $J = 16.4$ Hz, 1H), 7.16 (s, 1H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3): $\delta = 7.8, 31.6, 44.3, 45.9, 47.1, 51.7, 54.9, 66.4, 71.9, 78.5, 80.5, 100.9, 116.5, 118.2, 148.8, 158.1, 173.3$; HRMS (EI): m/z calcd for $\text{C}_{19}\text{H}_{24}\text{N}_3\text{O}_4\text{I}$ (M^+) 485.0812, found 485.0801; LRMS (EI): $m/z = 485$ (M^+ , 10), 386 (7), 358 (18), 150 (100), 99 (40).

Synthesis of substituted 11H-indolizino[1,2-b]quinolin-9-ones, ABCD tetracycles:

1. 1-Fluoro-11H-indolizino[1,2-b]quinolin-9-one (11c) and 3-fluoro-11H-indolizino[1,2-b]quinolin-9-one (11d): Use of the procedure described for the synthesis of **1a** with **9c**^[15c] (25.9 mg, 0.10 mmol) and 3-fluorophenyl isonitrile^[34a] (73 mg, 0.60 mmol) provided, after flash chromatography ($\text{CHCl}_3/\text{acetone}/\text{MeOH}$ 75:25:1) i) **11c** (less polar, 10.1 mg, 40%), as a white solid. M.p.: >260 °C; $^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta = 5.28$ (s, 2H), 6.74 (d, $J = 9.0$ Hz, 1H), 7.25–7.37 (m, 2H), 7.65–7.80 (m, 2H), 7.99 (d, $J = 8.6$ Hz, 1H), 8.61 (s, 1H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3): $\delta = 50.0, 101.3, 111.2$ (d, $J_{\text{CF}} = 19$ Hz), 121.0, 124.4, 125.4, 128.7, 129.8, 140.3, 145.6, 149.4, 153.8, 157.9 (d, $J_{\text{CF}} = 254$ Hz), 161.4; HRMS (EI): m/z calcd for $\text{C}_{15}\text{H}_9\text{FN}_2\text{O}$ (M^+) 252.0699, found 252.0697; LRMS (EI): $m/z = 252$ (M^+ , 100), 223 (53), 196 (7), 158 (8).

ii) **11d** (more polar, 6.2 mg, 25%), as a white solid. M.p.: >260 °C; $^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta = 5.25$ (s, 2H), 6.73 (d, $J = 9.1$ Hz, 1H), 7.28 (d, $J = 6.8$ Hz, 1H), 7.42 (td, $J_1 = J_2 = 8.5$ Hz, $J_3 = 2.5$ Hz, 1H), 7.67 (dd, $J = 9.1, 6.8$ Hz, 1H), 7.82 (dd, $J = 10.0, 2.3$ Hz, 1H), 7.90 (dd, $J = 9.1, 6.1$ Hz, 1H), 8.35 (s, 1H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3): $\delta = 49.8, 101.2, 113.2$ (d, $J_{\text{CF}} = 22$ Hz), 118.3 (d, $J_{\text{CF}} = 24$ Hz), 120.8, 125.0, 128.0, 129.9, 130.9, 140.3, 145.7, 150.2, 153.9, 161.5, 163.4 (d, $J_{\text{CF}} = 251$ Hz); HRMS (EI): m/z calcd for $\text{C}_{15}\text{H}_9\text{FN}_2\text{O}$ (M^+) 252.0699, found 252.0690; LRMS (EI): $m/z = 252$ (M^+ , 100), 223 (57), 196 (7), 158 (8).

2. 3-Amino-12-trimethylsilyl-11H-indolizino[1,2-b]quinolin-9-one (11f): Use of the procedure described for the synthesis of **1a** with **30**^[15c] (33.0 mg, 0.10 mmol) and **31** (65.0 mg, 0.3 mmol) provided **11e** (25.2 mg, 60%) as a yellow solid after flash chromatography ($\text{CHCl}_3/\text{MeOH}$ 95:5; $\text{CHCl}_3/\text{acetone}$ 4:1). HRMS (EI): m/z calcd for $\text{C}_{23}\text{H}_{27}\text{N}_3\text{O}_3\text{Si}$ (M^+) 421.1822, found 421.1838; LRMS (EI): $m/z = 421$ (M^+ , 46), 365 (100), 347 (32), 321 (95). A solution of this solid (17.2 mg, 0.041 mmol) in CH_2Cl_2 (500 μL) and TFA (120 μL) was stirred for 4 h at room temperature. The reaction mixture was poured into saturated NaHCO_3 (50 mL), extracted with AcOEt (4 \times 10 mL), and dried (Na_2SO_4). The residue obtained after evaporation of the solvents was purified by flash chromatography ($\text{CHCl}_3/\text{MeOH}$ 9:1) to give **11f** (9.8 mg, 75%) as a yellow solid. M.p.: >260 °C; $^1\text{H NMR}$ (300 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$ 4:1): $\delta = 0.49$ (s, 9H), 5.13 (s, 2H), 6.58 (dd, $J = 8.9, 1.0$ Hz, 1H), 6.98 (dd, $J = 9.2, 2.3$ Hz, 1H), 7.12 (d, $J = 2.3$ Hz, 1H), 7.25 (dd, $J = 7.1, 1.0$ Hz, 1H), 7.62 (dd, $J = 8.9, 7.1$ Hz, 1H), 7.89 (d, $J = 9.2$ Hz, 1H); $^{13}\text{C NMR}$ (75 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$ 4:1): $\delta = 1.3, 51.8, 101.4, 108.2, 118.9, 119.5, 125.9, 129.1, 141.2, 161.9$; HRMS (EI): m/z calcd for $\text{C}_{18}\text{H}_{19}\text{N}_3\text{OSi}$ (M^+) 321.1297, found 321.1307; LRMS (EI): $m/z = 321$ (M^+ , 100), 306 (10), 220 (11).

3. 1-Methyl-4-trimethylsilyl-11H-indolizino[1,2-b]quinolin-9-one (11g): Use of the procedure described for the synthesis of **1a** with **9c**^[15c] (78 mg, 0.30 mmol) and **35** (115 mg, 0.60 mmol) afforded a slightly yellow solid (44.3 mg, 46%) after flash chromatography ($\text{CHCl}_3/\text{MeOH}$ 95:5; $\text{CHCl}_3/\text{acetone}$ 3:1). M.p.: >260 °C; $^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta = 0.45$ (s, 9H), 2.68 (s, 3H), 5.21 (s, 2H), 6.68 (d, $J = 9.5$ Hz, 1H), 7.18 (d, $J = 7.1$ Hz, 1H), 7.37 (d, $J = 7.1$ Hz, 1H), 7.65 (dd, $J = 9.5, 7.1$ Hz, 1H), 7.79 (d, $J = 7.1$ Hz, 1H), 8.43 (s, 1H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3): $\delta = 0.1, 19.0, 50.2, 100.4, 120.1, 127.3, 127.7, 135.9, 136.4, 139.9, 140.4, 146.6, 151.0, 153.0, 161.6$; HRMS (EI): m/z calcd for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{OSi}$ (M^+) 320.1345, found 320.1358; LRMS (EI): $m/z = 320$ (M^+ , 27), 305 (100).

4. 1-Methyl-11H-indolizino[1,2-b]quinolin-9-one (11h): A mixture of **11g** (15.0 mg, 0.047 mmol) in AcOEt (200 μL) and 48% HBr (200 μL) was stirred for 18 h at room temperature. The final solution was poured into saturated NaHCO_3 (20 mL), extracted with AcOEt (4 \times 10 mL), and dried

(Na₂SO₄). The residue obtained after evaporation of the solvent was subjected to flash chromatography (CHCl₃/MeOH 95:5) to provide a white solid (10.3 mg, 86%). M.p.: 239–243 °C decomp.; ¹H NMR (300 MHz, CDCl₃): δ = 2.75 (s, 3H), 5.28 (brs, 2H), 6.72 (d, *J* = 9.0 Hz, 1H), 7.28 (d, *J* = 6.7 Hz, 1H), 7.44 (d, *J* = 6.7 Hz, 1H), 7.60–7.75 (m, 2H), 8.04 (d, *J* = 8.5 Hz, 1H), 8.51 (s, 1H); HRMS (EI): *m/z* calcd for C₁₆H₁₂N₂O (*M*⁺) 248.0950, found 248.0940; LRMS (EI): *m/z* = 248 (*M*⁺, 100), 219 (25).

5. 3-Fluoro-4-trimethylsilyl-11*H*-indolizino[1,2-*b*]quinolin-9-one (11*i*): Use of the procedure described for the synthesis of **1a** with **9c**^[15e] (25.9 mg, 0.10 mmol) and **39a** (77 mg, 0.40 mmol) afforded a slightly yellow solid (18.4 mg, 57%) after flash chromatography (CHCl₃/acetone 3:1). M.p.: > 260 °C; ¹H NMR (300 MHz, CDCl₃): δ = 0.53 (d, *J* = 1.9 Hz, 9H), 5.24 (s, 2H), 6.70 (d, *J* = 9.0 Hz, 1H), 7.18 (d, *J* = 6.8 Hz, 1H), 7.29 (t, *J* = 8.7 Hz, 1H), 7.66 (dd, *J* = 9.0, 6.8 Hz, 1H), 7.86 (dd, *J* = 9.0, 6.1 Hz, 1H), 8.30 (s, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 1.5, 49.9, 100.7, 118.3 (d, *J*_{CF} = 28 Hz), 120.4, 123.0 (d, *J*_{CF} = 26 Hz), 124.9, 127.2, 131.0, 131.2, 140.4, 146.3, 152.2, 154.0, 161.6, 167.7 (d, *J*_{CF} = 248 Hz); HRMS (EI): *m/z* calcd for C₁₈H₁₇FN₂O₃Si (*M*⁺) 324.1094, found 324.1096; LRMS (EI): *m/z* = 324 (*M*⁺, 60), 309 (100), 280 (23), 247 (16).

6. 2,3-Methylenedioxy-4-trimethylsilyl-11*H*-indolizino[1,2-*b*]quinolin-9-one (11*j*): Use of the procedure described for the synthesis of **1a** with **9c**^[15e] (25.9 mg, 0.10 mmol) and **39b** (43.8 mg, 0.20 mmol) afforded a brown solid (20.7 mg, 59%) after flash chromatography (CHCl₃/acetone 5:1). M.p.: > 260 °C; ¹H NMR (300 MHz, CDCl₃): δ = 0.35 (s, 9H), 5.00 (s, 2H), 5.95 (s, 2H), 6.50 (d, *J* = 8.9 Hz, 1H), 6.93 (s, 1H), 7.04 (d, *J* = 7.1 Hz, 1H), 7.58 (dd, *J* = 8.9, 7.1 Hz, 1H), 7.95 (s, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 0.7, 50.0, 100.6, 101.1, 107.2, 115.3, 118.0, 125.7, 126.2, 129.2, 141.2, 147.2, 147.8, 148.4, 151.2, 156.3, 162.1; HRMS (EI): *m/z* calcd for C₁₉H₁₈N₂O₃Si (*M*⁺) 350.1087, found 350.1089; LRMS (EI): *m/z* = 350 (*M*⁺, 92), 335 (100), 305 (14), 208 (15).

7. 3-Fluoro-11*H*-indolizino[1,2-*b*]quinolin-9-one (11*k*): As for **11h**, TMS-deprotection of **11i** (13.2 mg, 0.041 mmol) afforded a slightly yellow foam (7.7 mg, 75%) after flash chromatography (CHCl₃/acetone/MeOH 100:50:1). ¹H NMR (300 MHz, CDCl₃/CD₃OD 5:1): δ = 5.07 (s, 2H), 6.54 (d, *J* = 9.0 Hz, 1H), 7.21 (d, *J* = 7.1 Hz, 1H), 7.26 (td, *J* = 8.3, 2.5 Hz, 1H), 7.55–7.65 (m, 2H), 7.79 (dd, *J* = 9.0, 6.0 Hz, 1H), 8.29 (s, 1H); HRMS (EI): *m/z* calcd for C₁₅H₉FN₂O (*M*⁺) 252.0699, found 252.0700; LRMS (EI): *m/z* = 252 (*M*⁺, 100), 223 (46).

8. 2,3-Methylenedioxy-1-indolizino[1,2-*b*]quinolin-9-one (11*l*): A solution of **11j** (16.8 mg, 0.048 mmol) in CH₂Cl₂ (500 μL), TFA (500 μL) and Et₃O (50 μL) was stirred for 5 days at room temperature. Same workup as for **11h** provided a white solid (13.4 mg, 100%) after flash chromatography (CHCl₃/MeOH 95:5). M.p.: > 260 °C; ¹H NMR (300 MHz, CDCl₃/CD₃OD 4:1): δ = 5.09 (s, 2H), 6.06 (s, 2H), 6.57 (d, *J* = 8.8 Hz, 1H), 7.06 (s, 1H), 7.21 (m, 1H), 7.32 (s, 1H), 7.62 (dd, *J* = 8.8, 7.1 Hz, 1H), 8.13 (s, 1H); ¹H NMR (300 MHz, CF₃COOD): δ = 5.72 (s, 2H), 6.30 (s, 2H), 7.42 (s, 1H), 7.46 (d, *J* = 8.8 Hz, 1H), 7.56 (s, 1H), 8.14 (d, *J* = 7.4 Hz, 1H), 8.31 (brt, 1H), 8.95 (s, 1H); ¹³C NMR (75 MHz, CF₃COOD): δ = 55.4, 99.3, 106.3, 107.7, 120.1, 131.3, 132.1, 141.5, 141.7, 142.0, 142.8, 148.7, 152.6, 161.3; HRMS (EI): *m/z* calcd for C₁₆H₁₀N₂O₃ (*M*⁺) 278.0691, found 278.0693; LRMS (EI): *m/z* = 278 (*M*⁺, 100), 249 (28), 220 (18), 192 (20).

Synthesis of (20*S*)-Camptothecin Derivatives:

1. Irinotecan 1d: Dry benzene (1.5 mL) was added to a pressure tube with pyridone **25a** (39 mg, 0.097 mmol) and the isonitrile **24** (93.9 mg, 0.3 mmol). Hexamethylditin (50.0 mg, 0.150 mmol) was added, and the tube was sealed under argon and was irradiated for 9 h at 80 °C with a 275 W GE sunlamp. The mixture was evaporated, dissolved in MeOH with a few drops of DMSO, and injected into a reverse phase HPLC. A gradient elution, [5:95 MeCN/H₂O (0.1% TFA) to 30:70 MeCN/H₂O (0.1% TFA)], over 40 min gave a semipurified grey solid after lyophilization. The grey solid was further purified (CH₂Cl₂/EtOH 70:30) on a chromatotron using a 1 mm plate to give **1d** (18 mg, 31%) as a yellow solid. [α]_D²⁰ = + 62.9 (*c* = 0.2, CHCl₃); IR (CHCl₃): $\tilde{\nu}$ = 3038, 3018, 2962, 2929, 1721, 1661, 1602, 1222, 1214 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 1.04 (t, *J* = 7.3 Hz, 3H), 1.38–1.50 (m, *J* = 7.3 Hz, 3H), 1.50–1.71 (m, 2H), 1.72–1.90 (m, 8H), 2.05–2.30 (m, 2H), 2.85–3.20 (m, 7H), 3.20–3.48 (m, 2H), 4.38–4.60 (m, 2H), 5.25 (s, 2H), 5.30 (d, *J* = 16.4 Hz, 1H), 5.74 (d, *J* = 16.4 Hz, 1H), 7.56 (dd, *J*₁ = 9.1 Hz, *J*₂ = 2.3 Hz, 1H), 7.63 (s, 1H), 7.82 (d, *J* = 2.3 Hz, 1H), 8.21 (d, *J* = 9.2 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 7.90, 12.1, 14.1, 22.7, 23.2, 26.7, 31.6, 43.8, 49.4, 49.9, 63.2, 66.3, 72.9, 98.0, 114.6, 118.5, 125.6, 127.3, 127.5,

131.9, 145.3, 146.9, 147.3, 150.0, 150.3, 151.7, 153.0, 157.7, 173.9; HRMS (EI): *m/z* calcd for C₃₃H₃₈N₂O₆ (*M*⁺) 586.2791, found 586.2810; LRMS (EI): *m/z* = 586 (*M*⁺), 542, 515, 501, 487, 457, 431, 413, 392, 362, 348, 331, 319, 303.

2. (20*S*)-10,11-Ethylenedioxy-7-(4-methylpyrazinomethyl)camptothecin and (20*S*)-9,10-ethylenedioxy-7-(4-methylpyrazinomethyl)camptothecin (1e and 1o, mixture 60:40, respectively): Use of the procedure described for the synthesis of **1a** with **25f** (50 mg, 0.103 mmol) and 3,4-ethylenedioxyphenyl isonitrile (**10**)^[34a] (33 mg, 0.205 mmol) afforded a mixture of the unseparable regioisomers (30 mg, 57%) as a yellow solid after flash chromatography (CH₂Cl₂/MeOH 4:1). ¹H NMR (300 MHz, CDCl₃): δ = 7.22 (d, *J* = 9.2 Hz, 1H), 7.50 (d, *J* = 9.2 Hz, 1H), from H11 and H12 of **1o**; 7.05 (s, 1H), 7.35 (s, 1H), 7.42 (s, 1H), 7.43 (s, 1H), from H9 and H12 of **1e**, and H14 of both isomers; 5.14 (s, 2H) 5.20 (s, 2H) from H5 of both isomers; 4.9–5.5 (m, 4H) from H17 (-CH₂O-) of both isomers; 4.27 (m, 4H) 4.34 (brs, 4H) from ethylenedioxy (-OCH₂CH₂O-) of both isomers; 2.3–3.5 (m, 12H) from the piperazine ring and the methylene position linked to the piperazine ring of both isomers; 2.56 (s, 3H) 2.66 (s, 3H) from *N*-CH₃ of both isomers; 1.7 (m, 4H) from the methylene of Et of both isomers; 0.8 (m, 5H) from the methyl of Et of both isomers.

3. (20*S*)-10-Methoxycamptothecin (1f): Use of the procedure described for the synthesis of **1a** with **23** (43 mg, 0.12 mmol) and 4-methoxyphenyl isonitrile (**24a**)^[34a] (40 mg, 0.30 mmol) provided a white solid (22 mg, 51%) after flash chromatography (CHCl₃/MeOH 15:1). M.p.: 254–257 °C decomp.; [α]_D²⁰ = + 32.0 (*c* = 0.74, CHCl₃/MeOH 4:1); ¹H NMR (300 MHz, CDCl₃/CD₃OD 4:1): δ = 0.86 (t, *J* = 7.3 Hz, 3H), 1.78 (m, 2H), 3.23 (s, 1H), 3.82 (s, 3H), 5.08 (s, 2H), 5.13 (d, *J* = 16.3 Hz, 1H), 5.48 (d, *J* = 16.3 Hz, 1H), 7.03 (d, *J* = 2.7 Hz, 1H), 7.31 (dd, *J* = 9.3, 2.7 Hz, 1H), 7.89 (d, *J* = 9.3 Hz, 1H), 8.16 (s, 1H); ¹³C NMR (75 MHz, CDCl₃/CD₃OD 4:1): δ = 7.4, 31.1, 50.0, 55.4, 65.6, 72.7, 97.1, 105.3, 118.1, 123.8, 129.0, 129.6, 129.8, 130.2, 144.5, 146.1, 149.4, 151.1, 157.7, 158.9, 173.6; HRMS (EI): *m/z* calcd for C₂₁H₁₈N₂O₅ (*M*⁺) 378.1216, found 378.1204; LRMS (EI): *m/z* = 378 (*M*⁺, 78), 335 (100), 278 (88), 200 (56).

4. (20*S*)-10-Hydroxycamptothecin (1g): A solution of **1f** (2.7 mg, 0.0071 mmol) in 48% HBr (0.5 mL) was heated at 110 °C for 3 days in a sealed tube. The residue obtained after solvent removal was subjected to flash chromatography (CH₂Cl₂/acetone/MeOH 30:10:2) to provide a yellow solid (2.1 mg, 82%). [α]_D²⁰ = + 35.3 (*c* = 0.11, CH₂Cl₂/MeOH 4:1); ¹H NMR (300 MHz, CDCl₃/CD₃OD 5:1): δ = 0.92 (t, *J* = 7.4 Hz, 3H), 1.80 (m, 2H), 5.10 (s, 2H), 5.19 (d, *J* = 16.3 Hz, 1H), 5.56 (d, *J* = 16.3 Hz, 1H), 7.07 (d, *J* = 2.7 Hz, 1H), 7.33 (dd, *J* = 9.3, 2.7 Hz, 1H), 7.91 (d, *J* = 9.3 Hz, 1H), 8.11 (s, 1H); HRMS (EI): *m/z* calcd for C₂₀H₁₆N₂O₅ (*M*⁺) 364.1059, found 364.1049; LRMS (EI): *m/z* = 364 (*M*⁺, 40), 320 (100), 305 (31), 264 (47), 235 (26).

5. (20*S*)-7-Ethyl-10-methoxycamptothecin (1h): Use of the procedure described for the synthesis of **1a** with **25a** (40 mg, 0.10 mmol) and 4-methoxyphenyl isonitrile (**24a**)^[34a] (27 mg, 0.20 mmol) gave a white solid (23 mg, 57%) after flash chromatography (CHCl₃/MeOH 20:1). [α]_D²⁰ = + 19.1 (*c* = 0.11, CHCl₃/MeOH 4:1); ¹H NMR (300 MHz, CDCl₃/CD₃OD 10:1): δ = 0.91 (t, *J* = 7.4 Hz, 3H), 1.30 (t, *J* = 7.6 Hz, 3H), 1.81 (q, *J* = 7.6 Hz, 2H), 3.06 (q, *J* = 7.4 Hz, 2H), 3.88 (s, 3H), 5.12 (s, 2H), 5.18 (d, *J* = 16.1 Hz, 1H), 5.56 (d, *J* = 16.1 Hz, 1H), 7.21 (s, 1H), 7.36 (d, *J* = 9.3 Hz, 1H), 7.53 (s, 1H), 7.98 (d, *J* = 9.3 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃/CD₃OD 10:1): δ = 7.7, 13.4, 23.1, 31.4, 55.6, 66.0, 72.9, 98.0, 101.7, 118.1, 122.8, 127.3, 128.3, 131.5, 144.2, 145.1, 146.1, 149.3, 151.0, 157.8, 158.9, 173.8; HRMS (EI): *m/z* calcd for C₂₃H₂₂N₂O₅ (*M*⁺) 406.1529, found 406.1550; LRMS (EI): *m/z* = 406 (*M*⁺, 100), 378 (31), 362 (47), 306 (43).

6. (20*S*)-7-Ethyl-10-hydroxycamptothecin (1i): As for **1g**, hydrolysis of **1h** (15 mg, 0.037 mmol) provided a yellow solid (13 mg, 90%). M.p.: 215–217 °C decomp.; [α]_D²⁰ = + 29.3 (*c* = 0.45, CH₂Cl₂/MeOH 4:1); ¹H NMR (300 MHz, CDCl₃/CD₃OD 5:1): δ = 0.83 (t, *J* = 7.4 Hz, 3H), 1.19 (t, *J* = 7.6 Hz, 3H), 1.75 (q, *J* = 7.6 Hz, 2H), 2.95 (q, *J* = 7.4 Hz, 2H), 5.08 (s, 2H), 5.12 (d, *J* = 16.1 Hz, 1H), 5.47 (d, *J* = 16.1 Hz, 1H), 7.20 (s, 1H), 7.22 (d, *J* = 9.3 Hz, 1H), 7.45 (s, 1H), 7.85 (d, *J* = 9.3 Hz, 1H); HRMS (EI): *m/z* calcd for C₂₂H₂₀N₂O₅ (*M*⁺) 392.1372, found 392.1338; LRMS (EI): *m/z* = 392 (*M*⁺, 37), 348 (100), 333 (36), 292 (40).

7. (20*S*)-7-[2-(2-Tetrahydropyranyloxy)-ethyl]camptothecin (1j) (mixture of tetrahydropyranyloxy isomers): Use of the procedure described for the synthesis of **1a** with **25b** (67.0 mg, 0.134 mmol) afforded a yellow foam (32.9 mg, 52%) after flash chromatography (CHCl₃/acetone 9:1 to 7:3). [α]_D²⁰ = + 28.5 (*c* = 0.5, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ = 1.01 (t,

$J = 7.3$ Hz, 3 H), 1.30–1.70 (m, 6 H), 1.90 (m, 2 H), 3.36 (m, 1 H), 3.40–3.60 (m, 3 H), 3.77 (m, 1 H), 3.92 (brs, 1 H), 4.16 (m, 1 H), 4.47 (br t, 1 H), 5.27 (d, $J = 16.4$ Hz, 1 H), 5.31 (s, 2 H), 5.72 (d, $J = 16.4$ Hz, 1 H), 7.62 (t, $J = 8.0$ Hz, 1 H), 7.65 (s, 1 H), 7.76 (t, $J = 7.3$ Hz, 1 H), 8.10 (d, $J = 8.0$ Hz, 1 H), 8.21 (d, $J = 8.0$ Hz, 1 H); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 7.8, 19.3, 25.1, 30.3, 30.5, 31.5, 50.2, 62.1, 62.3, 66.3, 72.7, 97.9, 98.9, 118.4, 123.6, 127.4, 127.7, 130.0, 130.6, 147.0, 149.3, 150.1, 157.6, 162.5, 176.4$; HRMS (EI): m/z calcd for $\text{C}_{27}\text{H}_{28}\text{N}_2\text{O}_6$ (M^+) 476.1947, found 476.1923; LRMS (EI): $m/z = 476$ (M^+ , 44), 432 (22), 392 (26), 376 (33), 347 (82), 331 (47), 319 (50), 310 (39), 243 (46), 231 (100), 217 (44).

8. (20S)-7-Azacamptothecin (1k): Use of the procedure described for the synthesis of **1a** with **25c** (38.2 mg, 0.102 mmol) afforded a slightly yellow solid (19.1 mg, 54 %) after flash chromatography ($\text{CHCl}_3/\text{acetone}$ 9:1 to 7:3). M.p.: $>260^\circ\text{C}$ [(RS) isomer: ref. [5f] 280–285 °C decomp.]; $[\alpha]_D^{20} = +29.0$ ($c = 0.1$, $\text{CHCl}_3/\text{CH}_3\text{OH}$ 4:1); ^1H NMR (300 MHz, CDCl_3): $\delta = 1.02$ (t, $J = 7.3$ Hz, 3 H), 1.88 (m, 2 H), 3.87 (brs, 1 H), 5.29 (d, $J = 16.6$ Hz, 1 H), 5.30 (brs, 2 H), 5.73 (d, $J = 16.6$ Hz, 1 H), 7.69 (s, 1 H), 7.85–7.95 (m, 2 H), 8.18 (m, 1 H), 8.23 (m, 1 H); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 7.7, 31.6, 50.5, 66.3, 72.5, 99.4, 129.4, 129.9, 131.0, 131.5, 149.7$; HRMS (EI): m/z calcd for $\text{C}_{19}\text{H}_{15}\text{N}_3\text{O}_4$ (M^+) 349.1063, found 349.1052; LRMS (EI): $m/z = 349$ (M^+ , 100), 320 (29), 305 (33), 290 (22), 276 (24), 249 (33), 220 (21).

9. (20S)-10-Acetyloxycamptothecin (11): Use of the procedure described for the synthesis of **1a** with **23** (26.1 mg, 0.070 mmol) and **24b** (29.0 mg, 0.18 mmol) gave a slightly yellow solid (18.0 mg, 63 %) after flash chromatography ($\text{CHCl}_3/\text{MeOH}$ 96:4; $\text{CHCl}_3/\text{acetone}$ 4:1 to 2:1). M.p.: 257–259 °C decomp.; $[\alpha]_D^{20} = +31.9$ ($c = 0.2$, $\text{CHCl}_3/\text{MeOH}$ 5:1); ^1H NMR (300 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$ 5:1): $\delta = 0.86$ (t, $J = 7.4$ Hz, 3 H), 1.76 (m, 2 H), 2.24 (s, 3 H), 5.12 (s, 2 H), 5.13 (d, $J = 16.4$ Hz, 1 H), 5.49 (d, $J = 16.4$ Hz, 1 H), 7.41 (dd, $J = 9.2, 2.6$ Hz, 1 H), 7.53–7.56 (m, 2 H), 8.02 (d, $J = 9.2$ Hz, 1 H), 8.26 (s, 1 H); ^{13}C NMR (75 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$ 5:1): $\delta = 7.8, 20.7, 31.1, 49.9, 65.6, 72.6, 98.6, 118.7, 118.8, 125.9, 128.4, 129.0, 130.4, 131.1, 149.4, 150.9, 157.6, 169.4, 173.4$; HRMS (EI): m/z calcd for $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}_6$ (M^+) 406.1165, found 406.1168; LRMS (EI): $m/z = 406$ (M^+ , 96), 364 (100), 335 (18), 320 (43).

10. (20S)-10-tert-Butyloxycarbonylamino-camptothecin (1m): Use of the procedure described for the synthesis of **1a** with **23** (35.0 mg, 0.094 mmol) and **24c** (61 mg, 0.28 mmol) provided a slightly yellow solid (25.3 mg, 58 %) after flash chromatography ($\text{CHCl}_3/\text{MeOH}$ 96:4; $\text{CHCl}_3/\text{acetone}$ 4:1). $[\alpha]_D^{20} = +32.7$ ($c = 0.15$, $\text{CHCl}_3/\text{MeOH}$ 5:1); ^1H NMR (300 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$ 4:1): $\delta = 0.86$ (t, $J = 7.4$ Hz, 3 H), 1.41 (s, 9 H), 1.75 (m, 2 H), 5.07 (s, 2 H), 5.12 (d, $J = 16.4$ Hz, 1 H), 5.48 (d, $J = 16.4$ Hz, 1 H), 7.49 (s, 1 H), 7.51 (brd, $J = 9.0$ Hz, 1 H), 7.87 (d, $J = 9.0$ Hz, 1 H), 8.06 (s, 1 H), 8.15 (s, 1 H), 8.61 (brs, 1 H); ^{13}C NMR (75 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$ 4:1): $\delta = 7.3, 17.5, 29.4, 31.0, 51.0, 65.7, 72.6, 98.1, 113.2, 118.2, 124.1, 128.9, 129.1, 130.5, 138.7, 144.8, 146.0, 149.9, 151.1, 153.3, 157.7, 173.5$; HRMS (EI): m/z calcd for $\text{C}_{25}\text{H}_{25}\text{N}_3\text{O}_6$ (M^+) 463.1743, found 463.1739; LRMS (EI): $m/z = 463$ (M^+ , 14), 407 (46), 363 (100), 319 (51), 263 (30).

11. (20S)-10-Aminocamptothecin (1n): A solution of **1m** (17.4 mg, 0.038 mmol) in CH_2Cl_2 (500 μL) and TFA (100 μL) was stirred for 3 h at room temperature. The reaction mixture was poured into saturated NaHCO_3 (50 mL), extracted with AcOEt (10 \times 10 mL), and dried (Na_2SO_4). The residue obtained after evaporation of the solvents was purified by flash chromatography ($\text{CHCl}_3/\text{MeOH}$ 9:1) to give a yellow solid (11.8 mg, 87 %). M.p.: $>260^\circ\text{C}$ (ref. [5g] $>250^\circ\text{C}$); $[\alpha]_D^{20} = +29.9$ ($c = 0.15$, $\text{CHCl}_3/\text{MeOH}$ 4:1); ^1H NMR (300 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$ 4:1): $\delta = 0.86$ (t, $J = 7.4$ Hz, 3 H), 1.75 (m, 2 H), 5.02 (s, 2 H), 5.12 (d, $J = 16.4$ Hz, 1 H), 5.49 (d, $J = 16.4$ Hz, 1 H), 6.80 (d, $J = 2.5$ Hz, 1 H), 7.12 (dd, $J = 9.1, 2.5$ Hz, 1 H), 7.43 (s, 1 H), 7.77 (d, $J = 9.1$ Hz, 1 H), 7.95 (s, 1 H); HRMS (EI): m/z calcd for $\text{C}_{20}\text{H}_{17}\text{N}_3\text{O}_4$ (M^+) 363.1219, found 363.1216; LRMS (EI): $m/z = 363$ (M^+ , 100), 319 (96), 263 (55).

12. (20S)-9-(1-tert-Butyldiphenylsilyloxyethyl)camptothecin (1p) and **(20S)-11-(1-tert-butylidiphenylsilyloxyethyl)camptothecin (1q):** Use of the procedure described for the synthesis of **1a** with **23** (74.6 mg, 0.20 mmol) and **28** (231 mg, 0.60 mmol) provided, after flash chromatography ($\text{CHCl}_3/\text{AcOEt}$ 7:3):

i) **1p** (less polar, 39.2 mg, 31 %), as an oil. $[\alpha]_D^{20} = +20.3$ ($c = 0.5$, CHCl_3); ^1H NMR (300 MHz, CDCl_3): $\delta = 0.95$ –1.10 (m, 12 H), 1.59 (dd, $J = 7.3$ Hz, 3 H), 1.88 (m, 2 H), 3.90 (brs, 1 H), 5.17 (s, 2 H), 5.29 (d, $J = 16.4$ Hz, 1 H), 5.42 (m, 1 H), 5.73 (d, $J = 16.4$ Hz, 1 H), 7.10 (d, $J = 7.3$ Hz, 2 H), 7.21 (d, $J = 7.6$ Hz, 1 H), 7.30–7.45 (m, 5 H), 7.50 (s, 1 H), 7.61 (t, $J = 7.6$ Hz, 1 H),

7.65–7.75 (m, 4 H), 8.08 (d, $J = 8.2$ Hz, 1 H), 8.66 (d, $J = 9.2$ Hz, 1 H); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 7.8, 19.2, 26.4, 29.9, 31.6, 36.4, 50.2, 66.3, 70.4, 72.7, 98.1, 104.7, 118.5, 125.0, 125.5, 127.3, 127.7, 128.6, 128.8, 129.6, 130.0, 133.0, 133.5, 135.7, 142.6, 146.5, 147.9, 149.2, 150.1, 151.6, 157.7, 173.9$; HRMS (EI): m/z calcd for $\text{C}_{37}\text{H}_{38}\text{N}_2\text{O}_5\text{Si}$ [$M - \text{CO}_2^-$] 586.2652, found 586.2667; LRMS (EI): $m/z = 630$ (M^+ , 13), 586 (10), 573 (100), 555 (18), 529 (72), 495 (18), 357 (20), 329 (54).

ii) **1q** (more polar, 34.9 mg, 28 %), as an oil. $[\alpha]_D^{20} = +27.6$ ($c = 0.5$, CHCl_3); ^1H NMR (300 MHz, CDCl_3): $\delta = 1.03$ (t, $J = 7.4$ Hz, 3 H), 1.08 (s, 9 H), 1.40 (d, $J = 6.3$ Hz, 3 H), 1.89 (m, 2 H), 3.80 (brs, 1 H), 5.06 (q, $J = 6.3$ Hz, 1 H), 5.28 (s, 2 H), 5.29 (d, $J = 16.4$ Hz, 1 H), 5.73 (d, $J = 16.4$ Hz, 1 H), 7.10 (m, 1 H), 7.21 (d, $J = 7.3$ Hz, 2 H), 7.30 (d, $J = 7.3$ Hz, 1 H), 7.35–7.47 (m, 3 H), 7.51 (d, $J = 7.7$ Hz, 2 H), 7.65–7.70 (m, 2 H), 7.73 (d, $J = 6.5$ Hz, 2 H), 7.84 (d, $J = 8.5$ Hz, 1 H), 8.05 (d, $J = 8.1$ Hz, 1 H), 8.33 (s, 1 H); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 7.8, 19.3, 27.0, 29.7, 31.6, 37.8, 50.1, 66.3, 71.5, 72.8, 75.8, 98.1, 103.2, 118.5, 125.4, 126.3, 127.1, 127.7, 128.1, 129.7, 130.7, 133.3, 134.0, 135.8, 146.5, 149.0, 149.3, 150.1, 152.3, 157.6, 173.9$; HRMS (EI): m/z calcd for $\text{C}_{34}\text{H}_{29}\text{N}_2\text{O}_5\text{Si}$ [$M - t\text{-Bu}^+$] 573.1846, found 573.1857; LRMS (EI): $m/z = 630$ (M^+ , 2), 586 (9), 573 (92), 555 (13), 529 (100), 495 (18), 451 (18), 357 (15), 329 (47).

13. (20S)-9-Methyl-12-trimethylsilycamptothecin (1r): Use of the procedure described for the synthesis of **1a** with **23** (35.0 mg, 0.093 mmol) and **35** (54.0 mg, 0.28 mmol) gave a slightly yellow solid (20.3 mg, 50 %) after flash chromatography ($\text{CHCl}_3/\text{MeOH}$ 96:4; $\text{CHCl}_3/\text{acetone}$ 4:1). M.p.: 229–231 °C decomp.; $[\alpha]_D^{20} = +30.0$ ($c = 1$, CHCl_3); ^1H NMR (300 MHz, CDCl_3): $\delta = 0.47$ (s, 9 H), 1.04 (t, $J = 7.4$ Hz, 3 H), 1.90 (m, 2 H), 2.70 (s, 3 H), 3.90 (brs, 1 H), 5.26 (brs, 2 H), 5.29 (d, $J = 16.3$ Hz, 1 H), 5.73 (d, $J = 16.3$ Hz, 1 H), 7.40 (d, $J = 7.1$ Hz, 1 H), 7.48 (s, 1 H), 7.82 (d, $J = 7.1$ Hz, 1 H), 8.48 (s, 1 H); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 0.0, 7.7, 18.9, 31.4, 50.2, 66.2, 72.7, 97.2, 118.1, 127.2, 127.5, 128.0, 136.6, 140.2, 147.0, 150.4, 153.1, 157.6, 173.8$; HRMS (EI): m/z calcd for $\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_5\text{Si}$ (M^+) 434.1662, found 434.1637; LRMS (EI): $m/z = 434$ (M^+ , 39), 419 (100), 390 (19), 375 (64).

14. (20S)-9-Methylcamptothecin (1s): A solution of **1r** (23.2 mg, 0.053 mmol) in 48 % HBr (1.0 mL) was stirred for 3 h at 75 °C. The reaction mixture was poured into saturated $\text{NaHCO}_3/\text{brine}$ 1:1 (60 mL), extracted with AcOEt (5×15 mL), and dried. After evaporation of the solvent, the residue was purified by flash chromatography ($\text{CHCl}_3/\text{acetone}$ 4:1) to afford a slightly yellow solid (16.3 mg, 85 %). M.p.: 270–272 °C decomp. (ref. [5g] 278–280 °C); $[\alpha]_D^{20} = +38.6$ ($c = 0.15$, $\text{CHCl}_3/\text{MeOH}$ 4:1); ^1H NMR (300 MHz, CDCl_3): $\delta = 1.04$ (t, $J = 7.4$ Hz, 3 H), 1.88 (m, 2 H), 2.73 (s, 3 H), 3.92 (brs, 1 H), 5.28 (brs, 2 H), 5.28 (d, $J = 16.3$ Hz, 1 H), 5.72 (d, $J = 16.3$ Hz, 1 H), 7.44 (d, $J = 7.0$ Hz, 1 H), 7.66 (s, 1 H), 7.66 (dd, $J = 8.5, 7.0$ Hz, 1 H), 8.05 (d, $J = 8.5$ Hz, 1 H), 8.51 (s, 1 H); ^{13}C NMR (75 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$ 10:1): $\delta = 7.5, 18.7, 31.3, 50.2, 65.7, 72.7, 98.7, 118.8, 127.1, 127.6, 128.2, 128.6, 130.5, 135.0, 145.8, 148.7, 151.0, 151.4, 157.7$; HRMS (EI): m/z calcd for $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_4$ (M^+) 362.1267, found 362.1270; LRMS (EI): $m/z = 362$ (M^+ , 100), 333 (41), 318 (40), 303 (28), 289 (26), 262 (48), 233 (38).

15. (20S)-11-Fluoro-12-trimethylsilycamptothecin (1t): Use of the procedure described for the synthesis of **1a** with **23** (37.3 mg, 0.10 mmol) and **39a** (77 mg, 0.40 mmol) gave a slightly yellow solid (28.1 mg, 64 %) after flash chromatography ($\text{CHCl}_3/\text{acetone}$ 6:1). $[\alpha]_D^{20} = +26.1$ ($c = 0.2$, CHCl_3); ^1H NMR (300 MHz, CDCl_3): $\delta = 0.54$ (d, $J = 1.8$ Hz, 9 H), 1.03 (t, $J = 7.4$ Hz, 3 H), 1.89 (m, 2 H), 3.91 (brs, 1 H), 5.25 (brs, 2 H), 5.28 (d, $J = 16.4$ Hz, 1 H), 5.71 (d, $J = 16.4$ Hz, 1 H), 7.31 (t, $J = 8.8$ Hz, 1 H), 7.47 (s, 1 H), 7.85 (dd, $J = 8.8, 6.1$ Hz, 1 H), 8.31 (s, 1 H); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 1.6, 7.7, 31.4, 50.0, 66.3, 72.7, 97.5, 118.7$ (d, $J_{\text{CF}} = 32$ Hz), 123.3 (d, $J_{\text{CF}} = 27$ Hz), 125.0, 127.1, 131.2, 146.7, 150.3, 151.7, 154.1, 157.6, 167.8 (d, $J_{\text{CF}} = 248$ Hz); HRMS (EI): m/z calcd for $\text{C}_{25}\text{H}_{23}\text{FN}_2\text{O}_4\text{Si}$ (M^+) 438.1411, found 438.1411; LRMS (EI): $m/z = 438$ (M^+ , 66), 423 (100), 394 (12), 379 (52), 293 (21).

16. (20S)-10,11-Methylenedioxy-12-trimethylsilycamptothecin (1u): Use of the procedure described for the synthesis of **1a** with **23** (37.3 mg, 0.10 mmol) and **39b** (43.8 mg, 0.20 mmol) afforded a slightly yellow solid (24.6 mg, 53 %) after flash chromatography ($\text{CHCl}_3/\text{acetone}$ 6:1). M.p.: 225–228 °C decomp.; $[\alpha]_D^{20} = +26.4$ ($c = 0.2$, CHCl_3); ^1H NMR (300 MHz, CDCl_3): $\delta = 0.51$ (s, 9 H), 1.02 (t, $J = 7.3$ Hz, 3 H), 1.89 (m, 2 H), 3.85 (brs, 1 H), 5.14 (brs, 2 H), 5.27 (d, $J = 16.2$ Hz, 1 H), 5.70 (d, $J = 16.2$ Hz, 1 H), 6.10 (s, 2 H), 7.03 (s, 1 H), 7.37 (s, 1 H), 8.04 (s, 1 H); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 1.1, 7.8, 31.4, 50.1, 66.3, 72.7, 96.4, 101.3, 103.5, 115.9, 117.2, 125.9, 126.6, 129.2, 136.1, 147.5, 148.1, 148.6, 150.3, 156.5, 157.6, 173.9$; HRMS (EI): m/z calcd for $\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_6\text{Si}$ (M^+) 464.1404, found 464.1391;

LRMS (EI): $m/z = 464$ (M^+ , 90), 449 (100), 435 (16), 420 (47), 405 (84), 320 (17).

17. (20S)-11-Fluorocamptothecin (1v): As for **11h**, TMS-deprotection of **1t** for 15 h gave a slightly yellow solid (17.2 mg, 85%) after flash chromatography ($\text{CHCl}_3/\text{acetone}/\text{MeOH}$ 100:50:1). M.p.: 248–251 °C decomp. (ref. [5c] 196–198 °C); $[\alpha]_D^{20} = +38.3$ ($c = 0.2$, $\text{CHCl}_3/\text{CH}_2\text{OH}$ 4:1); $^1\text{H NMR}$ (300 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$ 4:1): $\delta = 0.90$ (t, $J = 7.3$ Hz, 3H), 1.82 (m, 2H), 3.51 (brs, 1H), 5.19 (s, 2H), 5.20 (d, $J = 16.4$ Hz, 1H), 5.58 (d, $J = 16.4$ Hz, 1H), 7.36 (td, $J = 8.5, 2.5$ Hz, 1H), 7.60 (s, 1H), 7.71 (dd, $J = 9.8, 2.4$ Hz, 1H), 7.85 (dd, $J = 9.0, 6.0$ Hz, 1H), 8.35 (s, 1H); $^{13}\text{C NMR}$ (75 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$ 4:1): $\delta = 7.4, 31.2, 49.9, 65.6, 72.6, 98.8, 112.6$ (d, $J_{\text{CF}} = 21$ Hz), 118.5 (d, $J_{\text{CF}} = 25$ Hz), 119.0, 125.1, 130.1, 131.5, 145.4, 149.5, 150.8, 152.9, 157.6, 163.5 (d, $J_{\text{CF}} = 253$ Hz), 173.4; HRMS (EI): m/z calcd for $\text{C}_{20}\text{H}_{15}\text{FN}_2\text{O}_4$ (M^+) 366.1016, found 366.1011; LRMS (EI): $m/z = 366$ (M^+ , 100), 337 (34), 322 (90), 307 (35), 293 (35), 266 (59), 237 (49).

18. (20S)-10,11-Methylenedioxy camptothecin (1w): A solution of **1u** (24.7 mg, 0.053 mmol) in TFA (2 mL) was refluxed under Ar for 10 h. Same workup as for **11h** provided a slightly yellow solid (15.9 mg, 76%) after flash chromatography ($\text{CHCl}_3/\text{MeOH}$ 95:5). M.p.: >260 °C (ref. [5g] 270 °C); $^1\text{H NMR}$ (300 MHz, CF_3COOD): $\delta = 1.01$ (t, $J = 7.3$ Hz, 3H), 2.03 (m, 2H), 3.84 (brs, 1H), 5.46 (d, $J = 17.1$ Hz, 1H), 5.60 (brs, 2H), 5.80 (d, $J = 17.1$ Hz, 1H), 6.31 (s, 2H), 7.42 (s, 1H), 7.56 (s, 1H), 8.03 (s, 1H), 8.92 (s, 1H); HRMS (EI): m/z calcd for $\text{C}_{21}\text{H}_{16}\text{N}_2\text{O}_6$ (M^+) 392.1008, found 392.1010; LRMS (EI): $m/z = 392$ (M^+ , 100), 363 (29), 348 (86), 333 (36), 320 (32), 292 (65), 263 (47).

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