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Tandem Radical Reactions of Isonitriles with 2-Pyridonyl and Other Aryl Radicals: Scope and Limitations, and a First Generation Synthesis of (±)-Camptothecin

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Summary: Photolysis of *N*-propargyl-6-halo-2-pyridones and related aromatic halides in the presence of aryl isonitriles provides tetra- and penta-cyclic products in a single step by a sequence of radical addition to the isonitrile followed by two cyclizations. The scope and limitations of the process are described along with a first generation synthesis of racemic camptothecin. Copyright © 1996 Elsevier Science Ltd

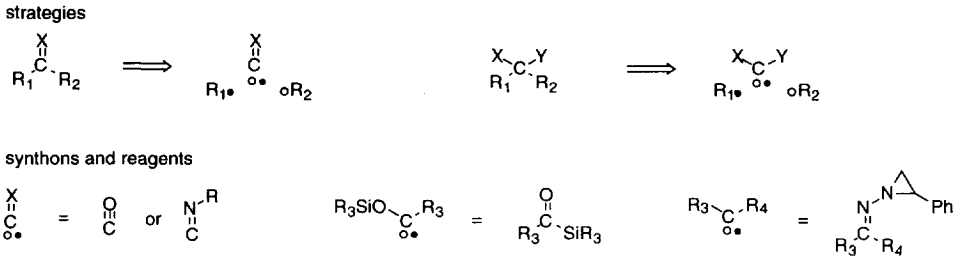
Introduction

Tandem radical reactions have established themselves as powerful tools for the synthesis of a diverse collection of organic molecules.[1] Generally speaking, the diversity comes not from the application of fundamentally different strategies, but from the wide tolerance of radical reactions (especially some classes of cyclizations) to substitutions of all sorts. The majority of tandem radical reactions are designed about a single strategy: the formation of vicinal carbon–carbon bonds.[1a] In this strategy, a C–C double (or triple) bond serves as the synthetic equivalent of a "vicinal radical acceptor/radical donor".[1a] Our early synthesis of hirsutene[2] shown in Figure 1 is a prime example of this strategy. Nuclear substitutions of one or more of the carbons can result in heterocycle synthesis. Retrosynthesis by this strategy has even been systematized by computer analysis.[3] New applications of this strategy appear regularly,[4] testifying to its generality and usefulness.

Figure 1. Forming Vicinal C–C Bonds by Tandem Radical Reactions

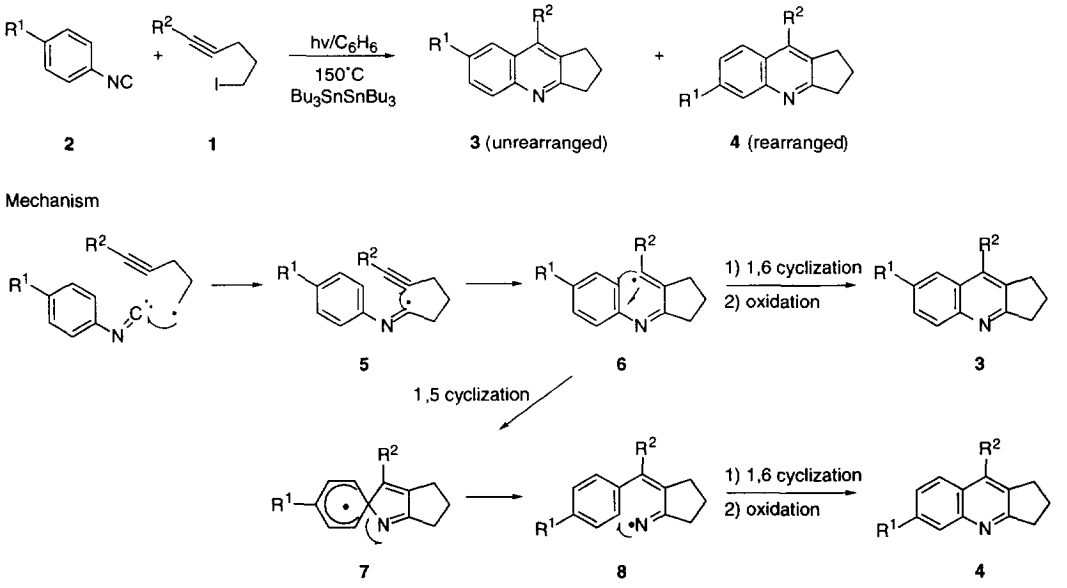
More recently, a number of types of tandem radical reactions that form non-vicinal bonds have been introduced. Dienes can be used to make 1,4 (vinylogously vicinal) carbon–carbon bonds,[5] and sequences involving fragmentations allow other options.[6] Several methods to form geminal carbon–carbon bonds have also been developed over the last several years.[7] Figure 2 summarizes these methods, which are based on isonitriles,[8,9] carbon monoxide,[10] acylsilanes,[11] and aziridinyl imines.[12] These methods for geminal bond formation form the nucleus of an emerging general strategy that complements the vicinal strategy outlined in Figure 1.[5]

Figure 2. Forming Geminal C–C Bonds by Tandem Radical Reactions



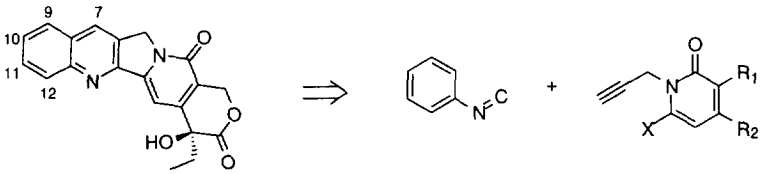
In 1991, we reported the first tandem reactions forming geminal carbon–carbon bonds.[8] We discovered that reactions of 5-iodo-1-pentynes **1** with aryl isonitriles **2** produced cyclopentaquinolines in reasonable yields (50-70%) under the optimized conditions shown in Figure 3.[8] The reaction was very general with respect to substitution on both partners; however, substituted aryl isonitriles tended to give mixtures of major unrearranged products **3** (80-90%) and minor, rearranged products **4** (10-20%). Figure 3 summarizes the current mechanistic understanding of the reaction.[5,6] Radical addition to the isonitrile to give **5** and cyclization provide the vinyl radical **6**. This "4 +1 radical annulation" forms the geminal carbon–carbon bonds. 1,6-Cyclization followed by oxidation provides the unrearranged product **3**. Evidence from Tundo's work[13] and ours suggests that the rearranged product **4** comes from 1,5-cyclization to spiro radical **7**, followed by opening of this to an iminyl radical **8**, reclosure, and finally oxidation. There are quite a number of possibilities for the final oxidation step, and it is not known with certainty how this is occurring.[9,14] Very recently, Nanni, Tundo and coworkers have reported the first trimolecular version of this type of sequence.[9]

Figure 3. Synthesis of Cyclopentaquinolines from Aryl Isonitriles and Iodopentynes



This paper reports the extension of the basic reaction in Figure 3 to include aryl- and heteroaryl-alkynes and nitriles. This work was inspired by the structure of camptothecin (**9**), the parent of a very important class of antitumor agents.[15] The structure of camptothecin and the strategic plan for synthesis are outlined in Figure 4. The first section of the paper describes our study of the scope and limitations of the reaction. Because of the interest in camptothecin, much of this work was conducted with *N*-propargyl-2-pyridones, but a number of systems have also been studied to show generality. Most of this work has not been previously communicated. The second part of the paper provides full details of our "first generation" camptothecin synthesis, the essence of which has been communicated.[16] Taken together, this work provided the foundation for our recently communicated "second generation" synthesis.[17] Work in the camptothecin area is ongoing, and full details of the second generation synthesis will be reported separately.

Figure 4. Camptothecin: Structure and Strategy

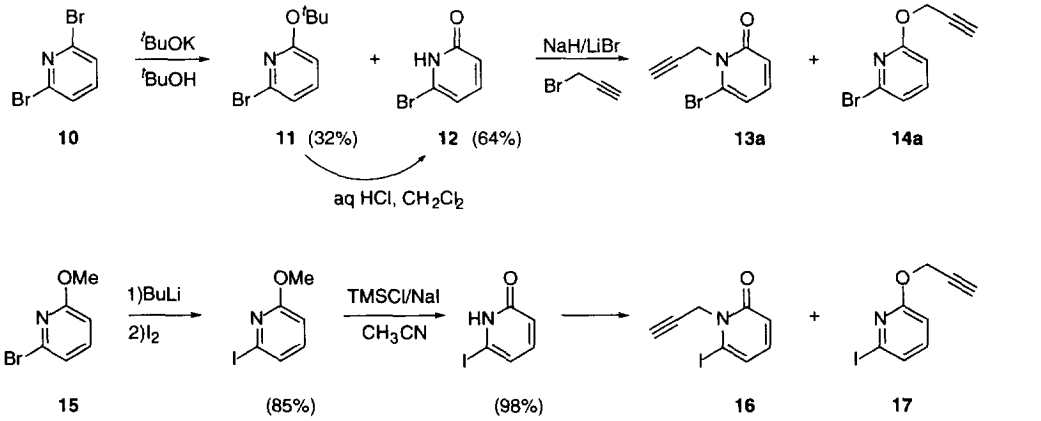


(20*S*)-camptothecin (**9**)

Results and Discussion

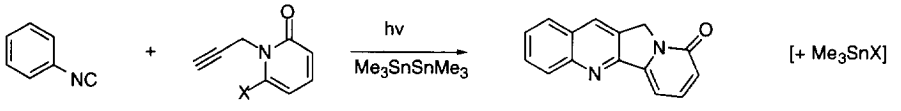
Scope and Limitations Studies: The plan outlined in Figure 4 was initially investigated with *N*-propargyl-6-bromo-2-pyridone (**13a**). This was prepared in two steps (eq 1) from commercially available 2,6-dibromopyridine (**10**). Reaction of this dibromide under the literature conditions[18] provided in our hands a mixture of 6-bromo-2-pyridone (**12**, 64%) and the intermediate *tert*-butyl ether **11** (32%). These were easily separated by chromatography, and the *tert*-butyl ether (**11**) was converted to the pyridone **12** by treatment with HCl. Propargylation under conditions optimized for reaction on nitrogen[19] gave **13a** and **14a** in a ratio of about 15/1. Competing *N*- versus *O*-alkylation

eq 1



is a problem for essentially all of the substrates reported in this work; however, under the best conditions,[19] the *N/O* alkylation ratios usually exceeded 10/1. In later work, we investigated the iodo analog **16**, which was readily prepared by lithiation of 6-bromo-2-methoxypyridine (**15**) and quenching with I_2, followed by demethylation with TMSI and *N*-propargylation. Optimized reaction conditions for the reactions of bromide **13a** and iodide **16** with phenyl isonitrile are shown in eq 2. The product of these reactions is known tetracycle **18a**[20] that possesses the A-D rings of camptothecin. In general, a 0.05 M benzene or *tert*-butanol solution containing **13a** or **16**, 2-3 equiv of phenyl isonitrile, and 1.5 equiv of hexamethylditin was warmed to 80 °C and irradiated with a UV lamp or a sunlamp. After 18-24 h, the mixture was cooled and the solvent was removed. The crude product **18a** was then purified by flash chromatography to determine the yield. Reactions did not contain significant amounts of other low molecular weigh products (other than volatile trimethyltin bromide or iodide). That **18a** can be prepared in only three steps from a simple bromopyridine is a testament to the power of this class of tandem radical reaction.

eq 2



18a

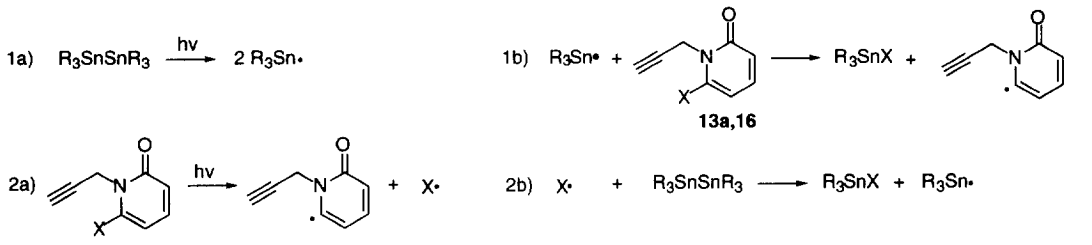
	X	conditions	yield
13a	Br	C_6H_6, UV	57%
16	I	C_6H_6, UV	80%
16	I	t-BuOH, sun lamp	95%

A large number of trial runs were conducted with phenyl isonitrile and bromide **13a** and isolated yields ranged from 20 to about 60%. In lieu of reporting all the experiments, we summarize the trends and conclusions. The high temperatures and large excess of isonitrile used in the original work[8] were found not to be crucial in reactions with **13a**. As the reaction temperature rises much above 100 °C, the yield actually starts to decline, possibly due to the thermal instability of phenyl isonitrile. A reduction in excess of phenyl isonitrile was compensated for increasing the reaction concentration. A concentration of about 0.05 M seems to be about optimal; above that, yields decline (again perhaps due to the self-reactions of the isonitrile). Either a sunlamp or a UV lamp can be used; the UV lamp is preferred for reactions in benzene while the sunlamp suffices for the reactions in *tert*-butanol. Yields in benzene and *tert*-butanol were roughly comparable. Most reactions were run in benzene; however, because benzene is not a suitable solvent for industrial applications, later work has focused on using *tert*-butanol. Many other solvents can be used for the reaction, but yields are usually lower, probably due to competing hydrogen abstraction reactions of the 2-pyridonyl radical from the solvent.

The addition of a reagent like hexamethylditin is important for obtaining clean reactions and good yields. Hexabutylditin is almost as good, but the purified yields are slightly lower. Perhaps this is because more material loss attends the DBU workup[21] and chromatographic purification required for the non-volatile tin compounds. While the ditin is important, its role is not completely clear. Two possibilities are shown in Figure 5. Ditin may serve as a source for trialkyltin radicals through photolytic cleavage of the tin–tin bond.[22] These tin radicals will then abstract a halide from the precursor **13a,16**. Alternatively, the 2-pyridonyl radicals may be generated by direct photolysis of the precursor, and the ditin may be a scavenger for bromine or iodine atoms. Ditin is also a good

scavenger for dibromine or diiodine, which are typical products when halides are irradiated.[22] Attempts to deliberately generate tin radicals by the sensitized photolysis of ditin[23] did not provide improved yields. Following radical generation, the mechanism for formation of the product is closely analogous to that shown in Figure 3.

Figure 5. Possibilities for Radical Generation



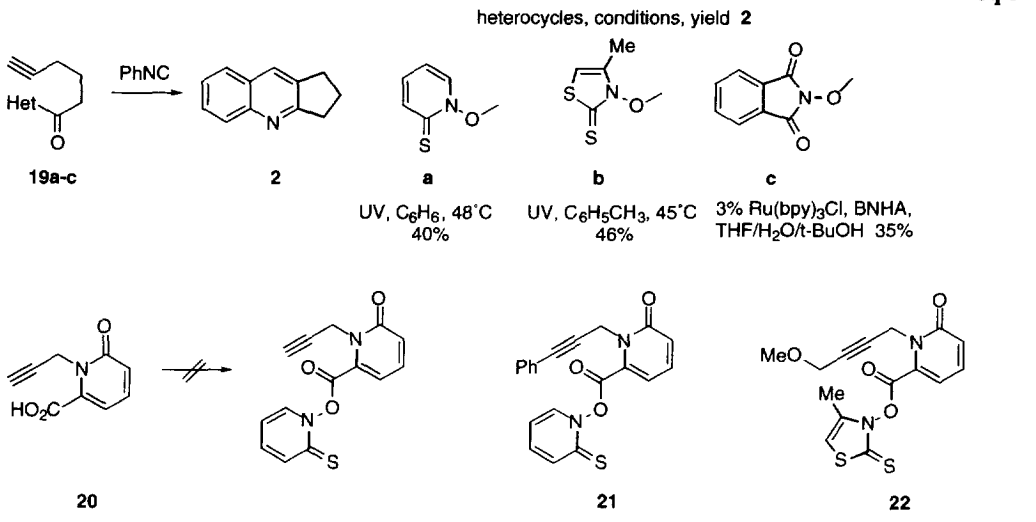
Compounds of the general structure Me_3SnX (X = heteroatom) are the most toxic of all organotin compounds,[24] so we have investigated several other additives and procedures. Most of these were not useful. Among those that showed promise, hexamethyldisilane could be used in place of the ditin, with an attendant sacrifice in yield that varies with the amount of isonitrile. Under the standard conditions (**13a**, 2 equiv of isonitrile), the disilane for ditin substitution produced **18a** in 28% yield. This yield increased to 45% when 5 equiv of phenyl isonitrile was used. In recent work with more complex pyridones, hexamethyldisilane has been compared several times with the hexamethyldistannane; there is typically a 10% yield penalty for using the disilane.

The effects of the halogen precursor are quite significant. *N*-Propargyl-6-chloropyridone (not shown) is essentially useless in this reaction; only traces of tetracyclic products are produced.[25] The bromide **13a** produces reasonable yields, but the best yields are obtained with the iodide **16**. The very high yields obtained with iodide **16** and phenyl isonitrile (80-90%, eq 2) were not routinely obtained with other isonitriles (see below). However, the iodide precursor **16** often gives 10-20% higher yields in a given reaction than the bromide **13a**. This halogen effect was discovered only after most of the work in this paper was completed, so it seems probable that many of the yields reported herein for bromides could be increased by using iodides.

Some time was also invested in preparing and reacting carboxylate precursors, including thiohydroxamates[26] and *N*-acyloxyphthalimides.[27] Precursors **19a-c** can be used in the original reaction, as shown by the results in eq 3. Yields of **2** ranged from 35-46%, and none of these reactions was optimized. However, these successes did not translate into the pyridone system. Attempts to form the thiohydroxamate derivative of **20** were all unsuccessful. Starting from substituted propargyl derivatives, we were able to isolate a low yield of the desired thiohydroxamates **21** and **22**; however, photolysis of either of these with phenyl isonitrile did not produce any of the expected tetracycle. In contrast, experiments with the bromide analogs of **21** and **22** succeeded (see **13b** and **13d** in eq 4). Based on these results, further studies of acid precursors were abandoned.

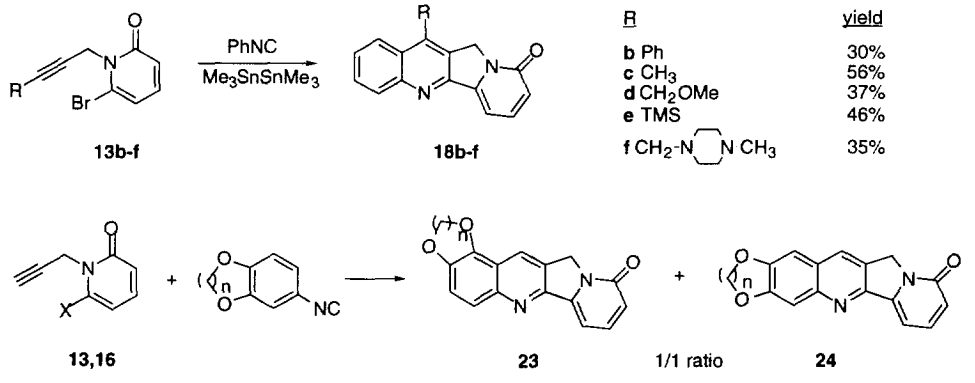
The series of experiments in eq 4 shows that wide latitude is possible at the terminal propargyl substituent. This position corresponds to C7 in camptothecin, and a number of important analogs with substituents at this position are known.[15] These reactions were all conducted under the optimized conditions with bromides **13b-f**, and isolated yields for **18b-f** of 30-56% were obtained.

eq 3



Variation of the isonitrile substituents was mostly studied with the more complex bromopyridone described in the next section. However, the reactions of **13a** and **16** with methylene- and ethylenedioxyphenyl isonitrile are informative. These isonitriles were again chosen because they represent important types of active camptothecin analogs.[28] The reactions provided separable 1/1 mixtures of two regioisomeric products **23** and **24**. Unlike the mixtures of products obtained in Figure 3, these products are both "unrearranged", and they result from direct 1,6-cyclization to the two non-equivalent ortho positions of the isonitrile. The reaction of the iodide **16** with the ethylenedioxyphenyl isonitrile was conducted with hexamethyldisilane instead of the distannane, and this provided a 65% yield of adducts **23/24**. This shows that the decrease in yield in going from the stannane to the silane can be partially compensated for by changing the bromide to an iodide.

eq 4



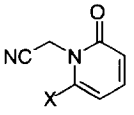
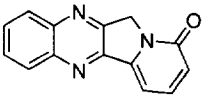
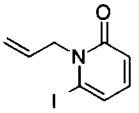
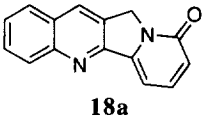
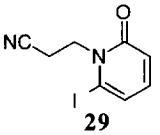
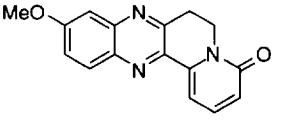
R	yield
b Ph	30%
c CH_3	56%
d CH_2OMe	37%
e TMS	46%
f CH_2-N⟨⟩N CH_3	35%

substrates	conditions	yield
n = 1, X = Br	ditin, UV, C_6H_6	37%
n = 2, X = Br	ditin, UV, C_6H_6	57%
	ditin, UV, t-BuOH	80%
n = 2, X = I	disilane, UV, t-BuOH	65%

The formation of two "unrearranged" products is typical for reactions of *meta*-substituted isonitriles. Significantly, no minor "rearranged" products were detected in this reaction or in any of the other reactions of meta-substituted isonitriles with *N*-propargylpyridones. The absence of the minor product is a major asset compared to the original reaction (Figure 3). We speculate that the rigidity of the *N*-propargylpyridone raises the energy of the transition state for 1,5-cyclization (leading to the spiro intermediate corresponding to **7**, Figure 3) relative to the transition state corresponding to 1,6-cyclization. Since 1,5-cyclization was already a minor path, only a relatively small increase in energy is needed for it to drop from competition.

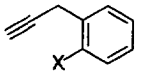
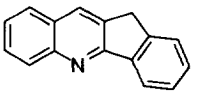
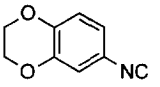
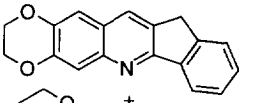
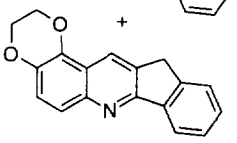
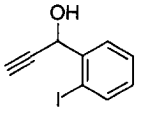
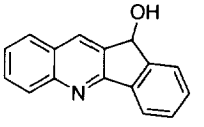
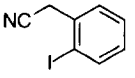
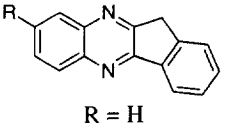
A number of other *N*-substituents were investigated besides propargyl, and Table 1 summarizes the results of these studies. The use of a nitrile acceptor (**25** and **26**) provided the interesting heterocycle **27** in poor yield starting from bromide **25** but in acceptable yield starting from iodide **26**. The use of the *N*-allyl derivative **28** provided the same product **18** as the *N*-propargyl precursors, though in lower yield. The intermediate dihydro product presumably suffered air oxidation during workup or chromatography. Addition of a methylene group to the nitrogen side chain might lead to formation of a 6-membered ring by a 5 + 1 annulation. However, this type of reaction has a problem: direct 5-*exo* cyclization of the initial pyridone radical with its own side chain is likely to compete very effectively with bimolecular addition to the isonitrile. Indeed, reaction of homologous nitrile **29** provided only 13% yield of the corresponding tetracycle **30**.

Table 1. Variation of the *N*-Substituent

entry	precursor	isonitrile	product	yield
		PhNC		
			27	
1	**25** X = Br			24%
2	**26** X = I			65%
3		PhNC		54%
	28		**18a**	
4		*p*-$CH_3OC_6H_4NC$		13%
	29		**30**	

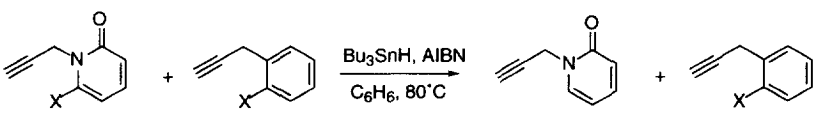
We also briefly investigated the use of benzenoid radicals in this tandem reaction, and the results of these experiments are summarized in Table 2. The aryl halides were noticeably less reactive than the halopyridones. Indeed, bromides were of little use in these reactions, requiring long times and producing only low product yields (see entry 1). Starting bromides were often present when the reactions were stopped. However, aryl iodides reacted at acceptable rates and provided modest to excellent yields of the corresponding tetracyclic products from both alkyne and nitrile acceptors (entries 2-5).

Table 2. Aryl Halide Precursors and Products

entry	precursor	isonitrile	product(s)	yield
				
1	X = Br	PhNC		8%
2	X = I	PhNC		95%
3	X = I		 + 	40% (1:1)
4		PhNC		35% (+ 63% recovered starting material)
5				
		PhNC	R = H	63%
		p-$CH_3OC_6H_4NC$	R = OMe	43%

The reduced reactivity of the aryl halides prompted the two competition experiments shown in eq 5. Reaction mixtures containing one equivalent each of the corresponding bromo- (or iodo-) pyridone and aryl bromide (or iodide) were reduced under standard conditions with only one equivalent of tributyltin hydride. In each experiment, the halopyridone was consumed, and the aryl halide was left intact. This suggests that the bromo- and iodopyridones are at least 50 times more reactive than their aryl analogs. While it is known that electron withdrawing substituents on aromatic rings increase the rate of halogen abstraction by tributyltin radicals, these polar effects are generally much smaller than 50.[29] Indeed, based on estimated rate constants for aryl iodides,[29] the iodopyridone **16** must react with tin radicals at rates approaching the diffusion controlled limit. One speculative explanation of this high reactivity is that the reaction occurs not by direct, concerted halogen abstraction, but instead by electron transfer from a tin radical to electron poor pyridone ring, followed by cleavage of the C–X bond of the resulting radical anion.[30]

eq 5

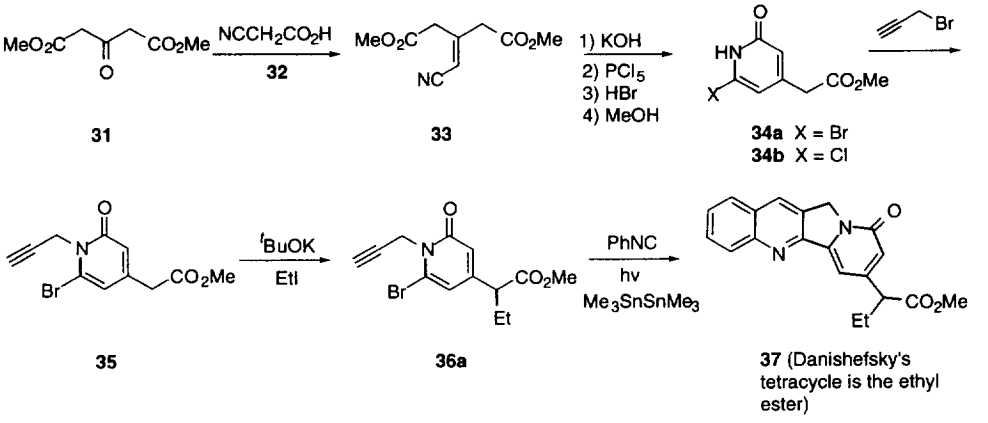


1 : 1

13 X = Br
16 X = I

Synthesis of Racemic Camptothecin: The "first generation" strategy for the synthesis of racemic camptothecin is summarized in Figure 4. The known "Danishefsky tetracycle" (**37**),[31] a popular intermediate in many of the early syntheses of camptothecin,[32,33] was selected as an initial target. The preparation of the requisite bromopyridone **36** for this strategy is summarized in Scheme 1.

Scheme 1



The synthesis of 6-bromopyridone **34a** was designed after a synthesis of 6-chloro-4-methylpyridone reported in 1970 by Simchen.[34] Doebner condensation of dimethylacetone dicarboxylate (**31**) and cyanoacetic acid (**32**) provided nitrile **33** in 70% yield. Saponification of the diester with potassium hydroxide presumably produced a diacid, which was immediately treated with phosphorous pentachloride in CH_2Cl_2. The solution containing the presumed acid chloride was cooled to –78 °C, and anhydrous HBr was introduced through a gas dispersion tube. The reaction was then quenched with methanol and worked up. Purification of crude product provided a 63% yield of bromopyridone **34a** contaminated with 3-5% chloropyridone **34b** (as determined by GC analysis). To prove the structure of **34b**, an authentic sample was made by following the Simchen procedure (substituting HCl for HBr), although the yield of this reference compound was only 11%. No attempt was made to remove the small amount of chloropyridone **34b** from **34a**.[35]

Bromopyridone **34a** was then propargylated under the optimized procedure[19] to provide a 12/1 mixture of the *N*- and *O*-propargylation products. Separation of these isomers by flash chromatography was very easy, and the *N*-propargyl bromopyridone **35** was isolated in 73% yield. Ethylation of **35** with potassium *tert*-butoxide and ethyl iodide in DME provided an 95% isolated yield of the mono-ethylated product **36a** alongside 3% of the diethylated product (not shown). Radical annulation of bromopyridone **36a** under the standard conditions provided the methyl ester analog **37** of the Danishefsky tetracycle in 45% isolated yield. Likewise, the ethyl ester (not shown, but prepared by a route analogous to the methyl ester) provided the actual Danishefsky tetracycle in 38% isolated yield.

The synthesis of racemic camptothecin was completed by following the procedures of Danishefsky.[31] Unfortunately, hydroxymethylation of **37** is not a very good reaction. The experiment summarized in eq 6 is typical of a number that we tried. Treatment of **37** with formaldehyde and sulfuric acid in refluxing dioxane for 17 h provided the desired lactone **38** in 22%

isolated yield. Other products included the regioisomeric lactone **39** (7%, also observed by Danishefsky), and the hydroxymethylated lactones **40** (10%) and **41** (6%). The major product was the hydrolyzed acid **42**, which could be esterified to give back **37**. The yield of lactone **38** based on recovered **37** was 35%. Despite extensive variations of reaction conditions, the isolated yield of **38** could not be improved significantly (the best isolated yield was 26%). Attempts to develop other methods to introduce the lactone were also unsuccessful. The air oxidation of **38** provides racemic camptothecin in quantitative yield.

eq 6

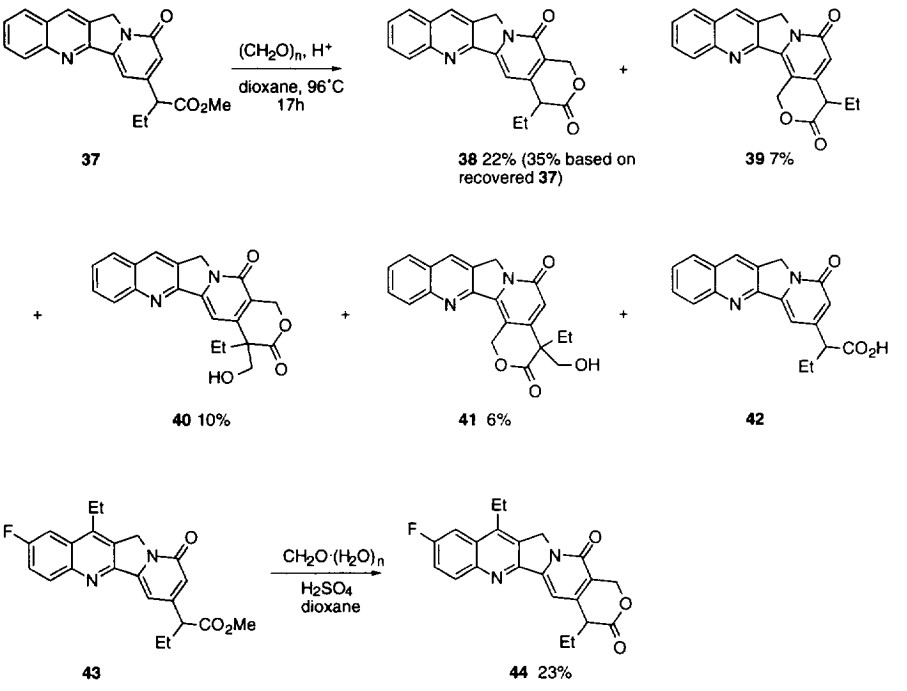
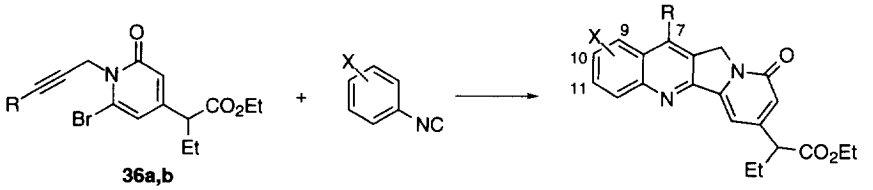


Table 3 shows the synthesis of a number of analogs of the Danishefsky tetracycle that were prepared from either the terminally unsubstituted or the ethyl-substituted propargyl derivatives **36a** and **36b**. The ethyl group was chosen because of the very high activity of 7-ethyl camptothecin and its derivatives.[36] *p*-Substituted isonitriles produced a single tetracyclic product, while *m*-substituted isonitriles produced inseparable mixtures of regioisomers in the indicated ratios. The yields of these reactions were not optimized.

Several hydroxymethylation reactions of the adducts in Table 3 were attempted under the conditions in eq 6, but in general, very complex reaction mixtures were produced, and we did not attempt purification. An exception was the hydroxymethylation of **43** (product of Table 3, entry 6), which was roughly analogous to that of the parent tetracycle and provided lactone **44** in 23% (eq 6). A number of other products (presumably analogous to **39**-**42**) were produced in this reaction, but we did not attempt to isolate and characterize them.

Table 3. Analogs of Danishefsky's Tetracycle



Entry	3 6	Pyridone	Isonitrile	Product(s)	Yields
1	**a**	R = H	*p*-F	10-F	33%
2	**a**	R = H	*p*-MeO	10-Me	33%
3	**a**	R = H	*p*-CF_3	10-CF_3	20%
4	**a**	R = H	*m*-CF_3	9/11-CF_3 (2/1)	22%
5	**a**	R = H	*m,p*-di-MeO	9,10/10,11-OMe (1/4)	42%
6	**b**	R = Et	*p*-F	10-F, 7-Et	36%

Conclusions

The results show that the radical annulation of 6-halo-*N*-propargyl-2-pyridones and related aryl radical precursors with aryl isonitriles is a remarkably powerful and general method to unite aryl rings with the formation of two new rings. The tolerance of diverse substituents on both partners is a graphic demonstration of the selectivity of radical reactions. Yields of the annulation products depend somewhat on the reaction conditions, but the largest single variable is the nature of the halogen precursor: iodides are significantly preferred over bromides. Chlorides, in turn, are not useful. The large beneficial effect of the iodide was not discovered until late in the study, after all of the work on the first generation synthesis of camptothecin had been completed. Were we to synthesize the iodide analog of bromopyridone **36**, the yields reported in eq 6 and Table 3 could surely be improved.

Even without using an iodide precursor, the synthesis of the Danishefsky tetracycle **37** is short and highly efficient. Of the six steps (Scheme 1) required to build the tetracycle from readily available dimethylacetone dicarboxylate, cyanoacetic acid, propargyl bromide, and phenyl isonitrile, five are directly concerned with building the molecular skeleton by synthesis of C–C or C–N bonds (or both). There are no oxidations or reductions, no protections or deprotections, and the only classical functional group transformation which does not directly aid in building the molecule is the hydrolysis of the diester to a diacid. (Some might not even count this as a "step", since the crude product was not characterized and was directly submitted to the next reaction.) The conversion of **37** to camptothecin then requires lactone formation and air oxidation (eq 6). Thus, the eight-step synthesis of camptothecin uses six steps to build the molecule and requires one functional group transformation and one oxidation. The remarkable efficiency of this synthesis results directly from the key radical reaction.

Efficiency notwithstanding, there is in the final analysis a fatal strategic flaw in this first generation synthesis: the Danishefsky tetracycle **37** is not a good intermediate for the synthesis of camptothecin and its analogs. There are three reasons for this conclusion. First, sequences that pass through the Danishefsky tetracycle are bound to make racemic camptothecin until a method of asymmetric hydroxylation is found for the last step. Given recent advances in asymmetric synthesis, this is probably a solvable problem (although the insolubility of **38** in many solvents may make finding a solution more difficult). Second, the yield of the hydroxymethylation step in its current

form is simply too low (<30%). Modest (even low) yields in complex steps like the radical annulation are acceptable because it would take many steps to replace them; however, low yields in a simple step like a hydroxymethylation are very unattractive. Despite extensive effort, we were not able to improve the yield of this step, though the possibility for improvement remains.

The biggest problem is the third one: the stringent (strongly acidic, high temperature) conditions required for hydroxymethylation are not tolerant of substituents in other parts of the molecule. At present, there is little current medicinal interest in 20(*S*)-camptothecin itself; interest instead focuses on an assortment of derivatives substituted at C-7, C-9, C-10 and C-11. Thus, the efficient synthesis of camptothecin itself is largely an academic goal. Expanding this to the realm of practicality requires that a synthesis of camptothecin be general and flexible. Syntheses passing through a Danishefsky tetracycle and requiring a late-stage hydroxymethylation by electrophilic aromatic substitution do not meet this requirement. In our first generation synthesis, the generality and flexibility of the key radical reaction are largely negated by the harsh conditions required for the subsequent hydroxymethylation.

Guided by this analysis, we designed, executed, and recently communicated[17] a second generation synthesis of camptothecin. The new synthesis is directly founded on the work reported in this paper, and it shows even better the power and generality of the key sequence of radical reactions.

The vast majority of known tandem radical reactions form vicinal bonds, and most of these make multiple five-membered rings. With the advent of methods to make geminal[8] (and other non-vicinal) bonds in radical reactions and with the expanded recognition that radical reactions can make other ring sizes besides five, the potential to design new sequences of radical reactions grows exponentially.

Experimental

General: All reactions were run under nitrogen or argon atmosphere. THF, toluene and benzene were distilled from sodium/benzophenone before use. Methylene chloride, DME, and DMF were distilled from calcium hydride. IR spectra were recorded in thin films deposited on NaCl plates. NMR spectra were observed in $CDCl_3$, unless otherwise noted (300 MHz for ^1H, 75 MHz for ^{13}C). All aryl isonitriles were prepared by Hoffman isonitrile synthesis.[37]

General Procedure for Preparation of Tetracycles by Radical Annulation of Halopyridones and Halobenzenes with Aryl Isonitriles. The reaction mixture of bromopyridone **13c** (65 mg, 0.29 mmol), phenyl isonitrile (0.90 mmol) and hexamethylditin (0.14 g, 0.43 mmol) in benzene (15 mL) was irradiated with UV lamp at 85 °C for 32 h. Benzene was removed in a reduced pressure and the residue was purified by column chromatography (acetone/$CHCl_3$ = 1.5 : 1) to provide the compound **18c** (40 mg) in 56% yield.

2-Iodo-6-methoxypyridine. To a stirred solution of 2-bromo-6-methoxypyridine (1.88 g, 10 mmol) in THF (15 mL) at –78 °C was added 1.6 N n-BuLi in hexanes (6.4 mL, 10 mmol). After 1 h at –78 °C iodine (2.80 g, 11 mmol) in THF (8 mL) was added and the resulting mixture was allowed to warm to room temperature. The solution was poured into 5% $Na_2S_2O_3$ (150 mL) and extracted with Et_2O (2 x 100 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated to provide 2.28 g (97%) of a white solid: m.p. 44-45 °C; ^1H NMR δ 3.86 (s, 3 H), 6.64 (d, J = 7.7 Hz, 1 H), 7.14 (t, J = 7.7 Hz, 1 H), 7.26 (d, J = 7.7 Hz, 1 H); ^{13}C NMR δ 54.2, 110.0, 113.9, 127.8, 139.8, 147.9, 163.5; HRMS (EI) *m/z* calcd for C_6H_6INO (M^+) 234.9494, found 234.9485.

6-Iodo-2-pyridone. To a mixture of 2-iodo-6-methoxypyridine (3.83 g, 16.3 mmol) and NaI (7.35 g, 50 mmol) in acetonitrile (25 mL) was slowly added chlorotrimethylsilane (6.50 mL, 50 mmol) then the reaction was stirred 6 h at 80 °C. After cooling to room temperature, the solution was poured into 5% $Na_2S_2O_3$ (150 mL) and brine (100 mL) and extracted with AcOEt (5 x 75 mL). The combined organic layers was dried and evaporated. The residue was subjected to flash chromatography (silica gel, $CHCl_3$/MeOH 92:8) to provide 3.11

g (86%) of a white solid: m.p. 150-152 °C; ^{1}H NMR ($CDCl_3/CD_3OD$ 4:1) δ 4.62 (br s, 1 H), 6.29 (d, J = 9.2 Hz, 1 H), 6.57 (d, J = 7.1 Hz, 1 H), 6.93 (dd, J = 9.2, 7.1 Hz, 1 H); ^{13}C NMR ($CDCl_3/CD_3OD$ 4:1) δ 97.0, 116.9, 119.7, 141.6, 164.9; HRMS (EI) *m/z* calcd for C_5H_4INO (M^+) 220.9338, found 220.9342.

6-Iodo-1-propargyl-2-pyridone (16):[19] ^{1}H NMR δ 2.33 (d, J = 2.5 Hz, 1 H), 5.07 (d, J = 2.5 Hz, 2 H), 6.51 (d, J = 9.2 Hz, 1 H), 6.80 (d, J = 7.0 Hz, 1 H), 6.96 (dd, J = 9.2, 7.0 Hz, 1 H); ^{13}C NMR δ 43.9, 73.0, 99.5, 120.0, 120.1, 140.1; HRMS (EI) *m/z* calcd for C_8H_6INO (M^+) 258.9494, found 258.9485.

1-(5-Hexynoyl)oxy-2(*1H*)-pyridonethione (19a). A solution of 5-hexynoic acid (0.20 g, 1.78 mmol) and $SOCl_2$ (0.78 mL, 10.7 mmol) in benzene (10 mL) was refluxed for 1 h. After removal of volatiles under reduced pressure, benzene (2 mL) was added to the residue and the solution was transfered to a mixture of *N*-hydroxypyridine-2-thione sodium salt (0.27 g, 1.78 mmol) and DMAP (22 mg, 0.18 mmol) in benzene (2 mL) in a flask wrapped with Al-foil at 0 °C. The reaction mixture was stirred for 3 h and washed with an ice-cold 10% $NaHSO_4$ (2 mL) solution and saturated NaCl solution (2 mL). The benzene layer was dried over $MgSO_4$ and concentrated. Column chromatography (SiO_2, CH_2Cl_2) gave a yellow, light sensitive product (0.43 mmol, 66%): ^{1}H NMR δ 1.99 (m, 3 H), 2.32 (m, 2 H), 2.80 (t, J = 7.3 Hz, 2 H), 6.61 (m, 1 H), 7.17 (m, 1 H), 7.59 (m, 2 H); ^{13}C NMR δ 17.57, 22.90, 30.16, 69.71, 82.56, 112.77, 133.77, 137.00, 137.62, 168.38, 174.46

1-(5-Hexynoyl)oxy-5-methylthiazoline-2(*1H*)thione (19b).
To a reaction mixture of 5-hexynoic acid (0.10 g, 0.89 mmol), 3-hydroxy-4-methyl-2(*3H*)thiazolethione (0.13 g, 0.90 mmol) and 4-pyrrolidinopyridine (20 mg, 0.13 mmol) in CH_2Cl_2 (5 mL) was added DCC (0.22 g, 0.99 mmol) at 0 °C in the dark. After 6 h at room temperature, CH_2Cl_2 was evaporated and diethyl ether (5 mL) was added. The resulting solid was filtered and diethyl ether was removed under vacuum. Purification by short silica gel column chromatography (Hex/EtOAc = 2:1) gave the product **19b** (0.11 g, 51%) as a yellow oil: ^{1}H NMR δ 2.02 (t, J = 2.7 Hz, 1 H), 2.03 (q, J = 7.2 Hz, 2 H), 2.16 (d, J = 1.1 Hz, 3 H), 2.38 (dt, J = 2.7, 6.9 Hz, 2 H), 2.85 (m, 2 H), 6.25 (d, J = 1.1 Hz, 1 H); ^{13}C NMR δ 13.39, 17.67, 23.19, 29.96, 69.94, 82.40, 102.58, 168.48, 180.71.

1-(5-Hexynoyl)oxyphthalimide (19c). To a solution of 5-hexynoic acid (0.50 g, 4.46 mmol), DMAP (60 mg, 0.49 mmol) and *N*-hydroxyphthalimide (0.77 g, 4.69 mmol) in CH_2Cl_2 (5 mL) was added DCC (1.01 g, 4.90 mmol) in one portion at room temperature. After 10 h, diethyl ether (10 mL) was added and the resulting precipitate was filtered. The solvent was removed under vacuum to give a residue which was purified by silica gel column chromatography (Et_2O/Hex = 1:1) to provide the product **19c** as an oil (1.02 g, 89%): ^{1}H NMR δ 2.01 (q, J = 5.6 Hz, 2 H), 2.03 (t, J = 2.6 Hz, 1 H), 2.36 (dt, J = 2.6, 6.8 Hz, 2 H), 2.82 (t, J = 7.4 Hz, 2 H), 7.81 (m, 4 H); ^{13}C NMR δ 17.60, 23.36, 29.66, 69.88, 82.46, 123.99, 128.82, 134.81, 161.91, 169.16; IR (neat, cm^{-1}) 3258, 1723, 1674, 1439, 1404, 1350, 1171, 1073, 967, 868; HRMS calcd for $C_{10}H_7NO_4$ (M – C_4H_4) 205.0375, found 205.0371

Cyclization Reaction of Barton Ester 19a with Phenyl Isonitrile: Synthesis of 2,3-Dihydro-*1H*-cyclopenta[b]quinoline (2). A mixture of the Barton ester **19a** (50 mg, 0.23 mmol) and phenyl isonitrile (0.92 mmol) in benzene (8 mL) was irradiated at room temperature with UV lamp for 1 h. Benzene was removed at reduced pressure and the residue was subjected to silica gel column chromatography to provide the known cyclized product **2** (23 mg, 60%): ^{1}H NMR δ 2.22 (quintet, J = 7.4 Hz, 2 H), 3.07 (dt, J = 7.4, 1.2 Hz, 2 H), 3.15 (t, J = 7.4, 2 H), 7.45 (td, J = 7.5, 1.0 Hz, 1 H), 7.62 (dt, J = 7.7, 1.3 Hz, 1 H), 7.74 (dd, J = 8.1, 1.3 Hz, 1 H), 7.90 (s, 1 H), 8.02 (d, J = 8.5 Hz, 1 H); ^{13}C NMR δ 23.29, 30.18, 34.32, 125.20, 127.11, 127.20, 128.04, 128.24, 129.98, 135.26, 147.19, 167.54; IR (neat, cm^{-1}) 3062, 2963, 1502, 1408; HRMS calcd for $C_{12}H_{11}N$ 168.0891, found 168.0891.

Cyclization Reaction of 1-(5-Hexynoyl)oxy-5-methylthiazoline-2(*1H*)thione (19b). A solution of 1-(5-hexynoyl)oxy-5-methylthiazoline-2(*1H*)thione (**19b**) (40 mg, 0.17 mmol) and phenyl isonitrile (0.68 mmol) in toluene (5 mL) was refluxed for 1 h. Solvent was removed and the residue was purified by silica gel column chromatography to give the compound **2** (13 mg, 46%).

Cyclization Reaction of 1-(5-Hexynoyl)oxyphthalimide (19c). Irradiation of a ^{t}BuOH-water (10 mL - 3 mL) solution of 1-(5-hexynoyl)-oxyphthalimide (**19c**) (50 mg, 0.19 mmol), phenyl isonitrile (0.97 mmol), 1-benzyl-1,4-dihydronicotinamide (50 mg, 0.23 mmol) and $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (5 mg, 0.0067 mmol) with 275W sun lamp for 12 h at 80 °C in a sealed tube produced the cyclized product **2** (12 mg, 35%).

12-Phenyl-11*H*-indolizino[1,2-b]quinolin-9-one (18b): ^{1}H NMR δ 5.07 (s, 2 H), 6.71 (d, J = 9.1 Hz, 1 H), 7.30 (d, J = 6.6 Hz, 1 H), 7.58 (m, 6 H), 7.66 (dd, J = 9.0, 6.9 Hz, 1 H), 7.80 (m, 2 H), 8.23 (d, J

= 6.6 Hz, 1 H); ^{13}C NMR δ 50.09, 101.00, 120.44, 126.01, 127.01, 127.36, 128.91, 129.23, 129.85, 130.14, 134.67, 140.43, 144.09, 146.58, 149.49, 152.43, 161.56; IR (neat, cm^{-1}) 1663, 1601, 1533, 1150, 790, 767, 719; HRMS calcd for $C_{21}H_{14}N_2O$, 310.1106, found 310.1082.

12-Methyl-11*H*-indolizino[1,2-b]quinolin-9-one (18c): ^{1}H NMR δ 2.75 (s, 3 H), 5.20 (s, 2 H), 6.72 (d, *J* = 8.9 Hz, 1 H), 7.25 (d, *J* = 7.2 Hz, 1 H), 7.64 (m, 2 H), 7.77 (dd, *J* = 8.1, 7.2 Hz, 1 H), 8.02 (d, *J* = 8.3 Hz, 1 H), 8.18 (d, *J* = 8.3 Hz, 1 H); ^{13}C NMR δ 15.34, 49.70, 76.67, 100.93, 120.34, 123.64, 127.43, 127.65, 127.91, 129.95, 130.30, 139.58, 140.40, 146.80, 148.84, 152.21, 161.65; IR (neat, cm^{-1}) 1653, 1575, 1158, 806, 761, 733; HRMS calcd for $C_{16}H_{12}N_2O$ 248.0950, found 248.0934.

12-Methoxymethyl-11*H*-indolizino[1,2-b]quinolin-9-one (18d): ^{1}H NMR δ 3.53 (s, 3 H), 4.97 (s, 2 H), 5,22 (s, 2 H), 6.66 (d, *J* = 9.4 Hz, 1 H), 7.17 (d, *J* = 7.3 Hz, 1 H), 7.60 (m, 2 H), 7.71 (t, *J* = 8.3 Hz, 1 H), 7.86 (d, *J* = 8.3 Hz, 1 H), 8.10 (d, *J* = 8.2 Hz, 1 H); ^{13}C NMR δ 50.48, 59.36, 69.94, 100.65, 120.37, 123.16, 125.42, 126.75, 127.56, 129.88, 130.18, 138.89, 140.23, 145.83, 148.53, 152.84, 161.46; IR (neat, cm^{-1}) 1662, 1593, 1120, 730; HRMS calcd for $C_{17}H_{14}N_2O_2$ 278.1055, found 278.1079.

12-Trimethylsilyl-11*H*-indolizino[1,2-b]quinolin-9-one (18e): ^{1}H NMR δ 0.62 (s, 9 H), 5.28 (s, 2 H), 6.69 (d, *J* = 8.6 Hz, 1 H), 7.24 (dd, *J* = 6.3, 0.7 Hz, 1 H), 7.62 (m, 2 H), 7.74 (dd, *J* = 7.7, 0.9 Hz, 1 H), 8.17 (d, *J* = 7.5 Hz, 1 H), 8.19 (d, *J* = 8.6 Hz, 1 H); ^{13}C NMR δ 1.65, 51.70, 100.48, 120.12, 126.94, 128.14, 129.37, 130.86, 131.79, 134.61, 140.30, 143.67, 146.09, 147.82, 151.33, 161.33; IR (neat, cm^{-1}) 1657, 1590, 1536, 1453, 1246, 843, 772; HRMS calcd for $C_{18}H_{18}N_2OSi$ 306.1188, found 306.1208.

12-(4-Methylpiperazin-1-ylmethyl)-11*H*-indolizino[1,2-b]quinolin-9-one (18f): ^{1}H NMR δ 2.32 (s, 3 H), 2.52 (br s, 4 H), 2.61 (br s, 4 H), 4.06 (s, 2 H), 5.36 (s, 2 H), 6.74 (d, *J* = 8.9 Hz, 1 H), 7.29 (d, *J* = 7.0 Hz, 1 H), 7.65 (m, 2 H), 7.79 (dd, *J* = 8.0, 6.9 Hz, 1 H), 8.20 (d, *J* = 7.5 Hz, 1 H), 8.35 (d, *J* = 8.3 Hz, 1 H); ^{13}C NMR δ 45.76, 50.24, 53.22, 54.85, 56.30, 100.90, 120.56, 124.40, 127.58, 127.71, 128.64, 130.07, 130.34, 139.69, 140.50, 146.45, 149.36, 152.69, 161.71; IR (neat, cm^{-1}) 3426, 1660, 1588, 1536, 1156, 807, 732; HRMS calcd for $C_{21}H_{22}N_4O$ 346.1794, found 346.1778.

1,2-Methylenedioxy-11*H*-indolizino[1,2-b]quinolin-9-one (23, n = 1): ^{1}H NMR δ 5.17 (s, 2 H), 6.18 (s, 2 H), 6.64 (d, *J* = 9.0 Hz, 1 H), 7.28 (d, *J* = 8.7 Hz, 1 H), 7.40 (d, *J* = 8.9 Hz, 1 H), 7.66 (m, 2 H), 8.30 (s, 1 H); ^{13}C NMR δ 49.85, 101.68, 102.65, 114.09, 114.33, 119.22, 122.58, 123.32, 127.91, 140.92, 141.14, 143.76, 144.67, 145.61, 150.39, 161.88; IR (neat, cm^{-1}) 1651, 1574, 1274, 1045, 783; HRMS calcd for $C_{16}H_{10}N_2O_3$ 278.0691, found 278.0689.

2,3-Methylenedioxy-11*H*-indolizino[1,2-b]quinolin-9-one (24, n = 1): ^{1}H NMR δ 5.09 (s, 2 H), 6.06 (s, 2 H), 6.58 (d, *J* = 9.0 Hz, 1 H), 7.06 (s, 1 H), 7.22 (d, *J* = 7.0 Hz, 1 H), 7.31 (s, 1 H), 7.63 (dd, *J* = 9.0, 7.0 Hz, 1 H), 8.13 (s, 1 H); ^{13}C NMR δ 49.96, 101.35, 102.33, 103.00, 104.55, 118.99, 125.96, 127.00, 127.50, 128.01, 130.08, 141.31, 146.20, 146.22, 146.94, 149.20, 149.75, 151.98; IR (neat, cm^{-1}) 1658, 1586, 1462, 1246, 1032, 774; HRMS calcd for $C_{16}H_{10}N_2O_3$ 278.0691, found 278.0689.

8,9-Dihydro-13*H*-7,10-dioxa-5,13a-diazaindeno[1,2-b]anthracen-11-one or 1,2-Ethylenedioxy-11*H*-indolizino[1,2-b]quinolin-9-one (23, n = 2): ^{1}H NMR δ 4.41 (m, 4 H), 5.17 (s, 2 H), 6.67 (d, *J* = 8.9 Hz, 1 H), 7.23 (d, *J* = 6.8 Hz, 1 H), 7.35 (d, *J* = 9.2 Hz, 1 H), 7.65 (d, *J* = 9.2 Hz, 1 H), 8.51 (s, 1 H); ^{13}C NMR δ 64.53, 101.00, 119.73, 120.67, 122.18, 122.98, 123.96, 127.94, 136.13, 140.37, 140.79, 144.40, 146.19, 150.68, 161.86; IR (neat, cm^{-1}) 1668, 1594, 1257, 778; HRMS calcd for $C_{17}H_{12}N_2O_3$ 292.0848, found 292.0833.

2,3-Dihydro-12*H*-1,4-dioxa-7,11a-diazaindeno[1,2-b]phenanthren-11-one or 2,3-Ethylenedioxy-11*H*-indolizino[1,2-b]quinolin-9-one (24, n = 2): ^{1}H NMR δ 4.27 (s, 4 H), 5.05 (s, 2 H), 6.56 (dd, *J* = 8.9, 0.9 Hz, 1 H), 7.17 (s, 1 H), 7.22 (dd, *J* = 7.2, 0.9 Hz, 1 H), 7.43 (s, 1 H), 7.61 (dd, *J* = 8.9, 7.2 Hz, 1 H), 8.09 (s, 1 H); ^{13}C NMR δ 64.25, 101.58, 112.03, 113.13, 119.02, 124.42, 126.81, 129.66, 141.27, 144.73, 145.57, 146.12, 148.00, 150.43, 162.07; IR (neat, cm^{-1}) 1662, 1599, 1248; HRMS calcd for $C_{17}H_{12}N_2O_3$ 292.0848, found 292.0817.

1-Cyanomethyl-6-iodo-2-pyridone (26):[19] ^{1}H NMR δ 5.17 (s, 1 H), 6.51 (dd, *J* = 9.3, 1.0 Hz, 1 H), 6.83 (dd, *J* = 7.0, 1.0 Hz, 1 H), 7.01 (dd, *J* = 9.3, 7.0 Hz, 1 H); ^{13}C NMR δ 41.7, 98.5, 113.9, 120.1, 120.6, 140.9, 161.5; HRMS (EI) *m/z* calcd for $C_7H_5IN_2O$ (M^+) 259.9447, found 259.9452.

11*H*-Indolizino[1,2-b]quinoxalin-9-one (27): ^{1}H NMR δ 5.27 (s, 2 H), 6.78 (d, *J* = 9.6 Hz, 1 H), 7.26 (d, *J* = 7.0 Hz, 1 H), 7.65 (dd, *J* = 9.6, 7.0 Hz, 1 H), 7.80-7.90 (m, 2 H), 8.10-8.20 (m, 2 H); ^{13}C

NMR δ 50.4, 102.2, 122.1, 129.3, 129.7, 130.8, 131.2, 140.0, 142.7, 152.8, 161.1; HRMS (EI) *m/z* calcd for $C_{14}H_9N_3O$ (M^+) 235.0746, found 235.0770.

1-Allyl-6-iodo-2-pyridone (28):[19] ^1H NMR δ 4.87 (dd, *J* = 3.9, 1.5 Hz, 2 H), 5.11 (dd, *J* = 17.0, 1.0 Hz, 1 H), 5.22 (dd, *J* = 10.4, 1.0 Hz, 1 H), 5.87 (m, 1 H), 6.45 (dd, *J* = 9.1, 1.0 Hz, 1 H), 6.75 (dd, *J* = 7.0, 1.0 Hz, 1 H), 6.88 (dd, *J* = 9.1, 7.0 Hz, 1 H); ^{13}C NMR δ 56.0, 100.9, 118.0, 119.8, 120.0, 131.1, 131.8, 162.2; HRMS (EI) *m/z* calcd for C_8H_8INO (M^+) 260.9651, found 260.9658.

1-(2-Cyanoethyl)-6-iodo-2-pyridone (29): A mixture of 6-iodo-2-pyridone (1.11 g, 5 mmol), acrylonitrile (0.47 mL, 7 mmol), K_2CO_3 (1.38 g, 10 mmol), LiBr (0.20 g, 2.3 mmol), n-Bu_4NBr (0.20 g, 0.65 mmol) in toluene (20 mL) and water (0.25 mL) was refluxed 4 h then filtered over Celite. The residue obtained after removal of the solvents was subjected to flash chromatography ($CHCl_3$/acetone 5:1) to provide 202 mg (15%) of a white solid: m.p. 119-123 °C; ^1H NMR δ 2.81 (t, *J* = 7.3 Hz, 2 H), 4.51 (t, *J* = 7.3 Hz, 2 H), 6.44 (d, *J* = 9.2 Hz, 1 H), 6.78 (d, *J* = 7.0 Hz, 1 H), 6.95 (dd, *J* = 9.2, 7.0 Hz, 1 H); ^{13}C NMR δ 16.2, 50.2, 100.2, 116.6, 120.2, 120.5, 140.5, 162.0; HRMS (EI) *m/z* calcd for $C_8H_7IN_2O$ (M^+) 273.9603, found 273.9612.

9-Methoxy-5,6-dihydro-4a,7,12-triaza-benzo[a]anthracen-4-one (30): ^1H NMR δ 3.39 (t, *J* = 6.6 Hz, 2 H), 3.98 (s, 3 H), 4.53 (t, *J* = 6.6 Hz, 2 H), 6.72 (dd, *J* = 8.6, 1.7 Hz, 1 H), 7.31 (d, *J* = 2.7 Hz, 1 H), 7.35-7.55 (m, 3 H), 7.97 (d, *J* = 9.2 Hz, 1 H); HRMS (EI) *m/z* calcd for $C_{16}H_{13}N_3O_2$ (M^+) 279.1008, found 279.1001.

1-(2-Bromophenyl)prop-2-yn-1-ol. To a solution of 2-bromobenzaldehyde (1.80 g, 9.73 mmol) in THF (30 mL) was added a 1 M solution of ethynylmagnesium bromide (25 mL) at room temperature. After 2 h, the mixture was diluted with diethyl ether (50 mL) and NH_4Cl solution (50 mL) was added. The organic layer was separated and the aqueous layer was reextracted with diethyl ether (30 mL). The combined organic layer was dried over $MgSO_4$ and concentrated. Short column chromatography (SiO_2, Hex/EtOAc = 3:1) of the residue gave the product as an oil (1.86 g, 91%): ^1H NMR δ 2.66 (d, *J* = 2.2 Hz, 1 H), 2.85 (br s, 1 H), 5.79 (d, *J* = 2.2 Hz, 1 H), 7.20 (td, *J* = 7.7, 1.1 Hz, 1 H), 7.36 (td, *J* = 7.7, 1.1 Hz, 1 H), 7.56 (dd, *J* = 7.9, 1.1 Hz, 1 H), 7.78 (dd, *J* = 7.7, 1.7 Hz, 1 H); ^{13}C NMR δ 64.05, 75.13, 82.42, 122.77, 128.01, 128.56, 130.21, 133.11, 138.94; IR (neat, cm^{-1}) 3291, 1466, 1437, 1269, 1190, 951, 754; HRMS calcd for C_9H_7BrO 209.9680, found 209.9688.

1-Bromo-2-(prop-2-ynyl)benzene (precursor in Table 2, entry 1):[38] Triethylsilane (0.86 mL, 5.38 mmol) and TFA (1.80 mL, 23.36 mmol) were added successively to a stirred solution of 1-(2-bromophenyl)prop-2-yn-1-ol (0.54 g, 2.60 mmol) in CH_2Cl_2 (20 mL) at room temperature. After stirring for 24 h, the reaction mixture was poured into saturated $NaHCO_3$ solution (50 mL). The organic layer was separated and dried over $MgSO_4$. Evaporation of solvents was followed by column chromatography (SiO_2, hexanes) gave the product (0.24 g, 47%): ^1H NMR δ 2.27 (t, *J* = 2.6 Hz, 1 H), 3.69 (d, *J* = 2.6 Hz, 2 H), 7.15 (td, *J* = 7.7, 1.2 Hz, 1 H), 7.32 (td, *J* = 7.7, 1.0 Hz, 1 H), 7.55 (dd, *J* = 7.7, 1.0 Hz, 1 H), 7.64 (dd, *J* = 7.7, 1.2 Hz, 1 H); IR (neat, cm^{-1}) 2923, 1468, 1024, 747; LRMS 196, 194, 115.

1-(2-Iodophenyl)prop-2-yn-1-ol (precursor in Table 2, entry 4): This compound was prepared by the method described for the preparation of the bromo alcohol in 95% yield: ^1H NMR δ 2.68 (d, *J* = 2.2 Hz, 1 H), 2.82 (br s, 1 H), 5.66 (d, *J* = 2.2 Hz, 1 H), 7.03 (td, *J* = 7.7, 1.7 Hz, 1 H), 7.40 (td, *J* = 7.7, 0.9 Hz, 1 H), 7.77 (dd, *J* = 7.9, 1.7 Hz, 1 H), 7.85 (dd, *J* = 7.7, 0.9 Hz, 1 H); ^{13}C NMR δ 68.14, 75.21, 82.63, 97.99, 128.01, 128.75, 130.19, 139.59, 141.89; IR (neat, cm^{-1}) 3292, 1437, 1011, 952, 752, 665, 639; HRMS calcd for C_9H_7IO 257.9542, found 257.9548.

1-Iodo-2-prop-2-ynylbenzene (precursor in Table 2, entry 2):[39] This known compound was prepared by the method described for the preparation of the bromo derivative in 51% yield: ^1H NMR δ 2.29 (t, *J* = 2.6 Hz, 1 H), 3.65 (d, *J* = 2.6 Hz, 1 H), 6.98 (t, *J* = 8.0 Hz, 1 H), 7.36 (t, *J* = 7.4 Hz, 1 H), 7.63 (d, *J* = 7.6 Hz, 1 H), 7.84 (d, *J* = 7.8 Hz, 1 H); IR (neat, cm^{-1}) 3300, 2954, 1462, 1013, 746; HRMS calcd for C_9H_7I 241.9593, found 241.9648.

11*H*-Indeno[1,2-b]quinoline (product in Table 2, entry 1): ^1H NMR δ 4.00 (s, 2 H), 7.51 (m, 4 H), 7.70 (d, *J* = 8.4 Hz, 1 H), 7.80 (dd, *J* = 8.0, 0.7 Hz, 1 H), 8.15 (s, 1 H), 8.22 (d, *J* = 8.4 Hz, 1 H), 8.32 (d, *J* = 8.6 Hz, 1 H); ^{13}C NMR δ 34.10, 122.15, 125.55, 125.75, 127.46, 127.62, 128.92, 129.14, 130.05, 131.28, 134.69, 140.40, 145.18, 148.10, 161.75; IR (neat, cm^{-1}) 3047, 2927, 1614, 1566, 1396, 1121, 948, 739; HRMS calcd for $C_{16}H_{11}N$ 217.0891, found 217.0875.

11*H*-Indeno[1,2-b]quinolin-11-ol (product in Table 2, entry 4): ^{1}H NMR δ (CD_3OD) 5.81 (s, 1 H), 7.50 (m, 3 H), 7.98 (d, J = 7.0 Hz, 1 H), 8.11 (d, J = 8.3 Hz, 1 H), 8.18 (d, J = 8.7 Hz, 1 H), 8.44 (s, 1 H); ^{13}C NMR δ 71.36, 121.47, 125.19, 126.04, 127.49, 128.17 (2 C), 129.30, 129.63, 130.82, 132.41, 137.97, 147.71, 148.00, 159.87; IR (neat, cm^{-1}) 3162, 1622, 1570, 1381, 1269, 1150, 1121, 1051, 826, 766, 745; HRMS calcd for $C_{16}H_{11}NO$ 233.0841, found 233.0814.

8,9-Ethylenedioxy-11*H*-indeno[1,2-b]quinoline (product in Table 2, entry 3): ^{1}H NMR δ 3.99 (s, 2 H), 4.40 (m, 4 H), 7.29 (d, J = 9.2 Hz, 1 H), 7.47 (m, 2 H), 7.57 (d, J = 6.7 Hz, 1 H), 7.74 (d, J = 9.2 Hz, 1 H), 8.26 (d, J = 8.3 Hz, 1 H), 9.41 (s, 1 H); ^{13}C NMR δ 34.19, 64.50, 64.60, 119.66, 120.86, 121.79, 121.99, 124.11, 125.43, 127.46, 129.60, 134.14, 136.23, 139.01, 140.49, 143.83, 144.86, 159.84; IR (neat, cm^{-1}) 1622, 1505, 1355, 1239, 1083, 786, 733; HRMS calcd for $C_{18}H_{13}NO_2$ 275.0946, found 275.0966.

7,8-Ethylenedioxy-11*H*-indeno[1,2-b]quinoline (product in Table 2, entry 3): ^{1}H NMR δ 3.96 (s, 2 H), 4.36 (s, 4 H), 7.20 (s, 1 H), 7.47 (m, 2 H), 7.57 (d, J = 7.6 Hz, 1 H), 7.65 (s, 1 H), 7.99 (s, 1 H), 8.25 (d, J = 6.5 Hz, 1 H); ^{13}C NMR δ 33.71, 64.18, 64.44, 111.77, 113.78, 121.44, 123.06, 125.13, 127.14, 129.24, 129.46, 132.03, 140.37, 143.41, 144.53, 145.99, 160.00; IR (neat, cm^{-1}) 2931, 1503, 1285, 1247, 1067, 758, 729; HRMS calcd for $C_{18}H_{13}NO_2$ 275.0946, found 275.0898.

(2-Iodophenyl)acetonitrile (precursor in Table 2, entry 5). A mixture of 2-iodobenzyl chloride (1.00 g, 3.96 mmol), KCN (0.39 g, 5.99 mmol) and Bu_4NI (0.15 g, 0.41 mmol) in DMSO (5 mL) was stirred at 60 °C for 4 h. The mixture was cooled to room temperature and poured into half saturated $NaHCO_3$ solution (20 mL). Extraction with diethyl ether (20 mL x 2) and drying ($MgSO_4$) was followed by short column chromatography (CH_2Cl_2/Hex = 1/1) to give the product as an oil (0.90 g, 93%): ^{1}H NMR δ 3.81 (s, 2 H), 7.04 (t, J = 7.6 Hz, 1 H), 7.39 (t, J = 7.6 Hz, 1 H), 7.53 (d, J = 7.6 Hz, 1 H), 7.87 (d, J = 7.4 Hz, 1 H); ^{13}C NMR δ 29.93, 99.06, 117.15, 129.04, 129.86, 133.19, 139.73; IR (neat, cm^{-1}) 3057, 2360, 2342, 1466, 1437, 1411, 1015, 748; HRMS calcd for C_8H_6IN 242.9545, found 242.9528.

11*H*-Indeno[1,2-b]quinoxaline (product in Table 2, entry 5, R = H). ^{1}H NMR δ 4.12 (s, 2 H), 7.53 (m, 2 H), 7.64 (m, 1 H), 7.73 (m, 2 H), 8.09 (m, 1 H), 8.14 (m, 1 H), 8.24 (m, 1 H); ^{13}C NMR δ 35.97, 122.67, 125.81, 128.04, 128.82, 128.98, 129.23, 131.11, 138.04, 141.24, 142.05, 143.50, 154.63, 159.45; IR (neat, cm^{-1}) 1506, 1465, 1401, 1370, 1334, 1119, 775, 761, 734; HRMS calcd for $C_{15}H_{10}N_2$ 218.0844, found 218.0840.

8-Methoxy-11*H*-indeno[1,2-b]quinoxaline (product in Table 2, entry 5, R = OMe): ^{1}H NMR δ 3.93 (s, 3 H), 4.04 (s, 2 H), 7.34 (m, 2 H), 7.46 (m, 2 H), 7.57 (m, 1 H), 8.01 (d, J = 9.9 Hz, 1 H), 8.15 (m, 1 H); ^{13}C NMR δ 35.81, 55.58, 107.00, 121.57, 121.89, 125.49, 127.72, 129.92, 130.20, 137.62, 138.20, 142.50, 142.56, 152.24, 159.32, 159.81; IR (neat, cm^{-1}) 1619, 1503, 1384, 1327, 1278, 1231, 1204, 1185, 1146, 1121, 1094, 1030, 961, 826, 801, 787, 765; HRMS calcd for $C_{16}H_{12}N_2O$ 248.0950, found 248.0952.

Dimethyl 3-(cyanomethylene)pentanedioate (33). A flask equipped with a Dean-Stark water separator was charged with benzene (60 mL), dimethyl acetone-1,3-dicarboxylate (34.8 g, 0.2 mol), cyanoacetic acid (18.7 g, 0.22 mol), acetic acid (5.4 g, 0.09 mol), and ammonium acetate (3.1 g, 0.04 mol). The mixture was stirred for 5 min and then heated at 130-135 °C until no more water was collected (6 h, about 6 mL of water collected) After the mixture was cooled to room temperature, cold water was added. This mixture was then extracted twice with ether. The combined organic phase was washed with water, saturated sodium bicarbonate solution and brine, and dried over sodium sulfate. After removal of solvent, the crude product was distilled to give dimethyl acetone-1,3-dicarboxylate (1.5 g) and **33** (27.2 g, 104-124 °C/0.03 mm hg) as a colorless liquid in 69-72% yield: ^{1}H NMR δ 5.43 (1 H, s), 3.57 (3 H, s), 3.55 (3 H, s), 3.45 (2 H, s), 3.26 (2 H, s); ^{13}C NMR δ 168.8, 168.5, 151.7, 115.2, 102.6, 52.0 (2 C), 40.5, 38.8; IR (neat, cm^{-1}) 2224, 1738.

Methyl 6-bromo-1,2-dihydro-2-oxo-4-pyridineacetate (34a). To a 0 °C solution of **33** (7.88 g, 40 mmol) in absolute ethanol (160 mL) was added potassium hydroxide (10 g, 180 mmol) with stirring. After 2 d, the solvent was removed and ice-water (100 mL) was added. The mixture was then acidified to pH ≈ 1 by slowly adding 6 N HCl at 0 °C. The solution was saturated with sodium chloride, and extracted with ethyl acetate (70 mL x 4). The combined organic phase was dried over sodium sulfate. After solvent removal under reduced pressure (rotatory evaporator, then vacuum pump), 3-(cyanomethylene)pentanedioic acid (6.87 g) was collected as yellow or orange solids. The solids were crushed to powders. Methylene chloride (270 mL) was added. The mixture was cooled to 0 °C, and phosphorus pentachloride (17.1 g, 82 mmol) was added under argon. The suspension was stirred at 25 °C until all the white solids dissolved (3-9 h). The flask was cooled

with an acetone-dry ice bath, evacuated with an aspirator, and sealed. Anhydrous hydrogen bromide gas (about 10 L, 400 mmol) was introduced and absorbed by the solution. The flask was refilled with argon and then equipped with a drying-tube which was connected to a gas trap to absorb excess HBr. The solution was stirred at –78 °C for 1 h and at room temperature for 8 h. After cooling to –78 °C, anhydrous methanol (15.4 g, 48 mmol) was added in one portion. The solution was then slowly warmed to room temperature and stirred for 2 h. After addition of ice-water (150 mL), two layers were separated. The aqueous layer was extracted with methylene chloride (100 mL x 2). The combined organic phase was dried over sodium sulfate. After removal of solvent, the residue was applied to chromatography (silica gel, $CHCl_3$/EtOAc=3:1, 2:1) to give **34a** (6.2 g, 63% yield from **33**). The product contained 3-8% of the 6-chloro analog **34b** as detected by GC: ^{1}H NMR δ 11.82 (1 H, br), 6.81 (1 H, d, J = 0.8 Hz), 6.60 (1 H, d, J = 0.8 Hz), 3.73 (3 H, s), 3.53 (2 H, s); ^{13}C NMR δ 169.7, 165.1, 149.4, 132.0, 117.6, 113.5, 52.6, 40.3; IR (neat, cm^{-1}) 1728, 1647, 1592, 1451; MS (*m/e*) 247 (M), 245 (M), 188, 186, 166 (base peak); HRMS calcd for $C_8H_8O_3BrN$ 244.9687, found 244.9661.

Methyl 6-bromo-1,2-dihydro-2-oxo-1-(2-propynyl)-4-pyridineacetate (35). A solution of **34a** (12.3 g, 50 mmol) in anhydrous ethylene glycol dimethyl ether (DME, 150 mL) was cooled to –10 °C. Sodium hydride (60% suspension in mineral oil, 2.2 g, 55 mmol) was added in several portions under argon. The mixture was warmed to room temperature and stirred until hydrogen ceased to evolve (about 20 min at rt). Anhydrous lithium bromide (4.8 g, 55 mol) was added. After 20 min, propargyl bromide (80% in toluene, 11.9 g, 100 mmol) and DMF (3.7 g, 50 mmol) were added. The mixture was heated at 65 °C for 16 h. After removal of solvent, methylene chloride and water were added to the residue and the organic layer was separated. The aqueous layer was extracted with methylene chloride. The combined organic phase was washed with water and brine, and dried over sodium sulfate. After removal of solvent, a small amount of ether was added to the residue, and solids precipitated. The solids were filtered and rinsed with ether to give **35** (9.34 g). The filtrate was concentrated and column chromatographed (silica gel, hexane/ethyl acetate = 2:1) to give an additional 1.1 g of **35** as an off-white solid. The total yield was 73%. The product contained 3-8% of the 6-chloro analog as detected by GC: m.p. 109-12 °C; ^{1}H NMR δ 6.50 (1 H, d, J = 1.6 Hz), 6.43 (1 H, d, J = 1.6 Hz), 5.02 (2 H, d, J = 2.4 Hz), 3.72 (3 H, s), 3.40 (2 H, s), 2.29 (1 H, t, J = 2.4 Hz); ^{13}C NMR δ 169.6, 161.7, 146.7, 126.3, 118.9, 112.9, 76.9, 72.6, 52.5, 40.1, 38.2; IR (neat, cm^{-1}) 3287, 1734, 1655, 1597; MS (*m/e*) 285 (M), 283 (M, base peak), 226, 224, 204, 176, 116; HRMS calcd for $C_{11}H_{10}O_3BrN$ 282.9844, found 282.9850.

(±)-Methyl 6-bromo-α-ethyl-1,2-dihydro-2-oxo-1-(2-propynyl)-4-pyridineacetate (36a). Under argon, **35** (852 mg, 3 mmol) was dissolved in DME (15 mL). The solution was cooled to –60 °C, and potassium *tert*-butoxide (353 mg, 3.15 mmol) was added. After 5 min at –60 °C, the mixture was warmed to –15° C, then recooled to –60 °C. Ethyl iodide (1.87 g, 12 mmol) was added. After 5 min at –60 °C, the reaction mixture was kept in an ice-bath, and stirred overnight (0 °C, slowly warming to room temperature). The solvent was removed, and methylene chloride (30 mL) and water (30 mL) were added. The organic layer was separated, and the aqueous layer was extracted with methylene chloride. The combined organic phase was washed with brine, and dried over sodium sulfate. After removal of solvent, the residue was chromatographed (silica gel, chloroform) to give **36a** (890 mg, 95% yield). The product contained 5-10% of the 6-chloro analog as detected by GC: ^{1}H NMR δ 6.52 (1 H, d, J = 1.7 Hz), 6.44 (1 H, d, J = 1.7 Hz), 5.01 (2 H, d, J = 2.4 Hz), 3.69 (3 H, s), 3.22 (1 H, t, J = 7.6 Hz), 2.30 (1 H, t, J = 2.4 Hz), 2.00 (1 H, m), 1.72 (1 H, m), 0.90 (3 H, t, J = 7.4 Hz); ^{13}C NMR δ 172.2, 161.7, 151.4, 126.3, 117.8, 111.3, 76.8, 72.5, 52.4 (2 C), 38.2, 25.3, 11.9; IR (neat, cm^{-1}) 3264, 1732, 1663, 1509; MS (*m/e*) 313 (M, base peak), 311, 284, 282, 254, 252, 232, 204, 144; HRMS calcd for $C_{13}H_{14}O_3BrN$ 311.0157, found 311.0139.

(±)-Methyl α-ethyl-9,11-dihydro-9-oxo-indolizino[1,2-b]quinoline-7-acetate (37). ^{1}H NMR δ 8.28 (1 H, s), 8.15 (1 H, d, J = 8.5 Hz), 7.84 (1 H, d, J = 8.2 Hz), 7.76 (1 H, t, J = 7.7 Hz), 7.58 (1 H, t, J = 7.5 Hz), 7.27 (1 H, d, J = 1.3 Hz), 6.61 (1 H, d, J = 1.3 Hz), 5.16 (2 H, s), 3.70 (3 H, s), 3.46 (1 H, t, J = 7.7 Hz), 2.14 (1 H, m), 1.88 (1 H, m), 0.94 (3 H, t, J = 7.4 Hz); ^{13}C NMR δ 172.7, 161.2, 152.8, 152.6, 148.7, 145.9, 130.9, 130.4, 129.6, 128.7, 128.1, 128.0, 127.7, 119.4, 101.0, 53.1, 52.3, 49.7, 25.6, 12.0; IR (neat, cm^{-1}) 2965, 2876, 1736, 1659, 1597, 1198, 1161; MS (*m/e*) 334 (M, base peak), 306, 275, 247; HRMS calcd for $C_{12}H_{18}O_3N_2$ 334.1317, found 334.1313.

(±)-Methyl α-ethyl-9,11-dihydro-2-fluoro-9-oxo-indolizino[1,2-b]quinoline-7-acetate (product in Table 3, entry 1): ^{1}H NMR δ 8.30 (1 H, s), 8.20 (1 H, dd, J = 9.3, 5.4 Hz), 7.55 (2 H, m), 7.29 (1 H, d, J = 1.3 Hz), 6.63 (1 H, d, J = 1.3 Hz), 5.24 (2 H, s), 3.71 (3 H, s), 3.48 (1 H, t, J = 7.7 Hz), 2.16 (1 H, m), 1.90 (1 H, m), 0.95 (3 H, t, J = 7.3 Hz); ^{13}C NMR δ 172.8, 161.3, 161.2 (J_{CF} = 250.8 Hz), 152.7, 152.5, 146.0, 145.7, 132.2 (J_{CF} = 8.3 Hz), 130.3, 129.7, 128.9 (J_{CF} = 10.2 Hz), 120.9 (J_{CF} = 26.8 Hz), 119.6, 111.3 (J_{CF} = 21.9 Hz), 100.9, 53.2, 52.4, 49.7, 25.7, 12.1; IR (neat, cm^{-1}) 1732, 1659, 1599; MS (*m/e*) 353 (M + 1), 352 (M, base peak), 324, 293, 265; HRMS calcd for $C_{20}H_{17}O_3FN_2$ 352.1224,

found 352.1248.

(±)-Methyl α-ethyl-9,11-dihydro-2-methoxy-9-oxo-indolizino[1,2-b]quinoline-7-acetate (Table 3, entry 2): ^{1}H NMR δ 8.16 (1 H, s), 8.03 (1 H, d, J = 9.3 Hz), 7.40 (1 H, dd, J = 9.3, 2.7 Hz), 7.21 (1 H, d, J = 1.0 Hz), 7.09 (1 H, d, J = 2.7 Hz), 6.58 (1 H, d, J = 1.0 Hz), 5.15 (2 H, s), 3.93 (3 H, s), 3.69 (3 H, s), 3.45 (1 H, t, J = 7.6 Hz), 2.11 (1 H, m), 1.90 (1 H, m), 0.93 (3 H, t, J = 7.3 Hz); ^{13}C NMR δ 172.7, 161.3, 158.7, 152.7, 150.4, 146.2, 144.9, 130.9, 129.4, 129.3, 123.4, 118.7, 105.4, 100.4, 96.1, 55.6, 53.2, 52.3, 49.7, 25.6, 12.0; IR (neat, cm^{-1}) 1730, 1667, 1601, 1240; MS (*m/e*) 364 (M, base peak), 336, 305, 278; HRMS calcd for $C_{21}H_{20}O_4N_2$ 364.1423, found 364.1477.

(±)-Methyl α-ethyl-2-trifluoromethyl-9,11-dihydro-9-oxo-indolizino[1,2-b] quinoline-7-acetate (product in Table 3, entry 3): ^{1}H NMR δ 8.46 (1 H, s), 8.33 (1 H, d, J = 8.9 Hz), 8.23 (1 H, s), 7.97 (1 H, dd, J = 8.9, 1.6 Hz), 7.37 (1 H, d, J = 1.0 Hz), 6.68 (1 H, d, J = 1.0 Hz), 5.29 (2 H, s), 3.72 (3 H, s), 3.50 (1 H, t, J = 7.7 Hz), 2.18 (1 H, m), 1.91 (1 H, m), 0.97 (3 H, t, J = 7.4 Hz); ^{13}C NMR δ 172.7, 161.2, 155.1, 152.7, 149.8, 145.3, 131.9, 131.0, 130.1, 129.5 (q, J_{CF} = 33 Hz), 127.0, 126.2 (2 C), 123.8 (q, J_{CF} = 271 Hz), 120.4, 101.8, 53.2, 52.5, 49.7, 25.7, 12.1; IR (neat, cm^{-1}) 1732, 1667, 1605, 1171, 1123; MS (*m/e*) 403, 402 (M, base peak), 383, 374, 343, 328, 315; HRMS calcd for $C_{21}H_{17}O_3F_3N_2$ 402.1191, found 402.1199.

(±)-Methyl α-ethyl-1-trifluoromethyl-9,11-dihydro-9-oxo-indolizino[1,2-b]quinoline-7-acetate and (±)-Methyl α-ethyl-3-trifluoromethyl-9,11-dihydro-9-oxo-indolizino[1,2-b]quinoline-7-acetate (Table 3, entry 4). Separation was accomplished by MPLC (chloroform/ethyl acetate = 11:1, 2.5:1); more polar isomer, ^{1}H NMR δ 8.67 (1 H, s), 8.39 (1 H, d, J = 8.5 Hz), 8.01 (1 H, d, J = 7.3 Hz), 7.84 (1 H, t, J = 7.9 Hz), 7.34 (1 H, d, J = 1.4 Hz), 6.67 (1 H, d, J = 1.4 Hz), 5.29 (2 H, s), 3.72 (3 H, s), 3.49 (1 H, t, J = 7.7 Hz), 2.17 (1 H, m), 1.91 (1 H, m), 0.96 (3 H, t, J = 7.4 Hz); ^{13}C NMR δ 172.7, 161.2, 153.6, 152.7, 149.0, 145.2, 134.5, 130.3, 128.8, 127.6, 126.7 (q, J_{CF} = 31 Hz), 126.3, 124.2, 124.0 (q, J_{CF} = 272 Hz), 120.2, 101.5, 53.2, 52.4, 50.0, 25.7, 12.1; IR (neat, cm^{-1}) 1736, 1671, 1609, 1306, 1167, 1121; MS (*m/e*) 403, 402 (M, base peak), 374, 343, 328, 315; HRMS calcd for $C_{21}H_{17}O_3F_3N_2$ 402.1191, found 402.1162; less polar isomer, ^{1}H NMR δ 8.53 (1 H, broad s), 8.44 (1 H, s), 8.06 (1 H, d, J = 8.6 Hz), 7.82 (1 H, dd, J = 8.6, 1.4 Hz), 7.35 (1 H, d, J = 1.4 Hz), 6.69 (1 H, d, J = 1.4 Hz), 5.30 (2 H, s), 3.73 (3 H, s), 3.50 (1 H, t, J = 7.7 Hz), 2.18 (1 H, m), 1.92 (1 H, m), 0.97 (3 H, t, J = 7.4 Hz); ^{13}C NMR δ 172.6, 161.2, 154.4, 152.8, 147.9, 145.2, 132.2 (q, J_{CF} = 33 Hz), 131.0, 130.8, 129.4 (2 C), 127.6, 123.8 (q, J_{CF} = 271 Hz), 123.4, 120.2, 101.7, 53.2, 52.5, 49.8, 25.7, 12.1; IR (neat, cm^{-1}) 1736, 1665, 1592, 1325, 1188, 1165, 1129; MS (*m/e*) 403, 402 (M, base peak), 383, 374, 343, 328, 315; HRMS calcd for $C_{21}H_{17}O_3F_2N_3$ 402.1191, found 402.1177.

(±)-Methyl α-ethyl-2,3-dimethoxy-9,11-dihydro-9-oxo-indolizino[1,2-b]quinoline-7-acetate and (±)-Methyl α-ethyl-1,2-dimethoxy-9,11-dihydro-9-oxo-indolizino[1,2-b]quinoline-7-acetate (product in Table 3, entry 5). Separation was accomplished by MPLC (chloroform/ethyl acetate/methanol = 1:1:0, then 1:1:0.1); more polar isomer, ^{1}H NMR δ 8.19 (1 H, s), 7.51 (1 H, s), 7.22 (1 H, d, J = 1.1 Hz), 7.13 (1 H, s), 6.60 (1 H, d, J = 1.1 Hz), 5.20 (2 H, s), 4.08 (3 H, s), 4.06 (3 H, s), 3.71 (3 H, s), 3.47 (1 H, t, J = 7.7 Hz), 2.16 (1 H, m), 1.90 (1 H, m), 0.95 (3 H, t, J = 7.4 Hz); ^{13}C NMR δ 172.7, 161.4, 153.3, 152.7, 150.9, 150.5, 146.5, 146.1, 128.9, 127.6, 124.3, 118.6, 107.9, 105.2, 100.1, 56.3, 56.2, 53.2, 52.3, 49.8, 25.5, 12.0; IR (neat, cm^{-1}) 1736, 1667, 1617, 1599, 1503, 1431, 1256, 1225; MS (*m/e*) 395, 394 (M, base peak), 366, 335, 320, 308; HRMS calcd for $C_{22}H_{22}O_5N_2$ 394.1529, found 394.1521; less polar isomer ^{1}H NMR δ 8.63 (1 H, s), 7.98 (1 H, d, J = 9.4 Hz), 7.60 (1 H, d, J = 9.4 Hz), 7.26 (1 H, d, J = 1.5 Hz), 6.62 (1 H, d, J = 1.5 Hz), 5.24 (2 H, s), 4.05 (6 H, s), 3.71 (3 H, s), 3.47 (1 H, t, J = 7.8 Hz), 2.16 (1 H, m), 1.90 (1 H, m), 0.95 (3 H, t, J = 7.3 Hz); ^{13}C NMR δ 172.8, 161.4, 152.7, 151.2, 149.4, 146.1, 144.4, 142.1, 128.9, 125.8, 125.0, 124.1, 119.2, 118.7, 100.7, 61.5, 56.8, 53.2, 52.4, 50.0, 25.6, 12.1; IR (neat, cm^{-1}) 1732, 1662, 1595, 1267, 1169, 1096; MS (*m/e*) 395, 394 (M, base peak), 379, 366, 335, 308; HRMS calcd for $C_{22}H_{22}O_5N_2$ 394.1529, found 394.1550.

(±)-Methyl α,12-diethyl-2-fluoro-9,11-dihydro-9-oxo-indolizino[1,2-b]quinoline-7-acetate (product in Table 3, entry 6). ^{1}H NMR δ 8.18 (1 H, dd, J = 9.2, 5.6 Hz), 7.67 (1 H, dd, J = 9.9, 2.6 Hz), 7.54 (1 H, td, J = 9.2, 2.6 Hz), 7.28 (1 H, s), 6.62 (1 H, s), 5.19 (2 H, s), 3.70 (3 H, s), 3.47 (1 H, t, J = 7.7 Hz), 3.10 (2 H, q, J = 7.6 Hz), 2.14 (1 H, m), 1.90 (1 H, m), 1.36 (3 H, t, J = 7.6 Hz), 0.94 (3 H, t, J = 7.4 Hz); ^{13}C NMR δ 172.7, 161.3, 161.2 (J_{CF} = 250.2 Hz), 152.8, 151.9, 146.4, 146.3, 144.9, 133.0 (J_{CF} = 9.4 Hz), 127.8 (J_{CF} = 12.0 Hz), 127.7, 120.2 (J_{CF} = 26.3 Hz), 119.3, 107.3 (J_{CF} = 23.4 Hz), 100.9, 53.2, 52.3, 49.0, 25.6, 23.2, 13.8, 12.0; IR (neat, cm^{-1}) 1734, 1665, 1601; MS (*m/e*) 380 (M, base peak), 352, 321, 294; HRMS calcd for $C_{22}H_{21}O_3FN_2$ 380.1536, found 380.1539.

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References and Notes

1. a) Curran, D. P. *Synlett* **1991**, 63. b) Curran, D. P. In *Comprehensive Organic Synthesis*; B. M. Trost and I. Fleming, Ed.; Pergamon: Oxford, **1991**; Vol. 4; pp 779. c) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. d) Tietze, L. F.; Beifuss, U. *Angew. Chem. Int. Ed. Eng.* **1993**, *32*, 131. e) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103.
2. a) Curran, D. P.; Rakiewicz, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 1448. b) Curran, D. P.; Rakiewicz, D. M. *Tetrahedron* **1985**, *41*, 3943.
3. Mehta, G.; Barone, R.; Azario, P.; Barberis, F.; Arbelot, M.; Chanon, M. *Tetrahedron* **1992**, *48*, 8953.
4. Selected examples appearing during 1995: Busato, S.; Scheffold, R. *Helv. Chim. Acta* **1994**, *77*, 92. Matzeit, A.; Schafer, H. J.; Amatore, C. *Synthesis* **1995**, 1432. Bookermilburn, K. I.; Thompson, D. F. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2315. Bowman, W. R.; Stephenson, P. T.; Young, A. R. *Tetrahedron Lett.* **1995**, *36*, 5623. Woltering, T. J.; Hoffmann, H. M. R. *Tetrahedron* **1995**, *51*, 7389. Lopez, J. C.; Gomez, A. M.; Fraser-Reid, B. *J. Org. Chem.* **1995**, *60*, 3871. Parsons, P. J.; Penkett, C. S.; Cramp, M. C.; West, R. I.; Warrington, J.; Saraiva, M. C. *Synlett* **1995**, 507. Zoretic, P. A.; Zhang, Y. Z.; Ribeiro, A. A. *Tetrahedron Lett* **1995**, *36*, 2929. Nishida, A.; Ogasawara, Y.; Kawahara, N.; Nishida, M. *Tetrahedron Lett* **1995**, *36*, 3015. Myers, A. G.; Condroski, K. R. *J. Am. Chem. Soc.* **1995**, *117*, 3057. Feldman, K. S. *Synlett* **1995**, 217. Russell, G. A.; Li, C. Z.; Chen, P. *J. Am. Chem. Soc.* **1995**, *117*, 3645. Curran, D. P.; Sun, S. N. *Aust. J. Chem.* **1995**, *48*, 261.
5. Schwartz, C. E.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 9272.
6. Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, *93*, 2091.
7. Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, in press.
8. Curran, D. P.; Liu, H. *J. Am. Chem. Soc.* **1991**, *113*, 2127.
9. Nanni, D.; Pareschi, P.; Rizzoli, C.; Sgarabotto, P.; Tundo, A. *Tetrahedron* **1995**, *51*, 9045.
10. a) Ryu, I. *J. Syn. Org. Chem. Jpn.* **1992**, *50*, 737. b) Ryu, I; Sonoda, N. *Ang. Chem. Int. Ed.*, **1996**, in press.
11. a) Curran, D. P.; Jiaang, W.-T.; Palovich, M.; Tsai, Y.-M. *Synlett* **1993**, 403. b) Tsai, Y.-M.; Tang, K. H.; Jiaang, W.-T. *Tetrahedron Lett.* **1993**, *34*, 1303.
12. a) Kim, S.; Kee, I. S.; Lee, S. *J. Am. Chem. Soc.* **1991**, *113*, 9882. b) Kim, S.; Kee, I. S. *Tetrahedron Lett.* **1993**, *34*, 4213.
13. Leardini, R.; Nanni, D.; Pedulli, G. F.; Tundo, A.; Zanardi, G.; *J. Chem. Soc., Perkin Trans. 1* **1986**, 1591.
14. Bowman, W. R.; Heaney, H.; Jordan, B. M. *Tetrahedron* **1991**, *47*, 10119.
15. *Camptothecins: New Anticancer Agents* (Eds. Potmesil, M., Pinedo, H.), CRC Press, Boca Raton, 1995.
16. Curran, D. P.; Liu, H. *J. Am. Chem. Soc.* **1992**, *114*, 5863.
17. Curran, D. P.; Josien, H.; Ko, S.-B., *Ang. Chem. Int. Ed.* **1995**, *34*, 2683.
18. Newcome, G. R.; Broussard, J.; Staires, S. K.; Sauer, J. D. *Synthesis* **1974**, 707.
19. Liu, H.; Ko, S. B.; Josien, H.; Curran, D. P. *Tetrahedron Lett.* **1995**, *36*, 8917.
20. Kametani, T.; Nemoto, H.; Takeda, H.; Takano, S. *Tetrahedron* **1970**, *26*, 5753.
21. Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140.
22. Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc.* **1986**, *108*, 2489.
23. Harendza, M.; Junggebauer, J.; Lessmann, K.; Neumann, W. P.; Tews, H. *Synlett* **1993**, 286.

24. Pereyre, M.; Quiinard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: London, 1987, pp 342.
25. The best conditions for this reaction, photolysis in the presence of Et_3N, gave **18a** in 6-10% yield. See: Cossy, J. *Bull. Soc. Chim. France* **1994**, *131*, 344.
26. a) Barton, D. H. R.; Chern, C. Y.; Jaszberenyi, J. C. *Aust. J. Chem.* **1995**, *48*, 407. b) Barton, D. H. R. *Pure Appl. Chem.* **1994**, *66*, 1943.
27. a) Okada, K.; Okamoto, K.; Morita, N.; Okubo, K.; Oda, M. *J. Am. Chem. Soc.* **1991**, *113*, 9401. b) Okada, K.; Okubo, K.; Morita, N.; Oda, M. *Tetrahedron Lett.* **1992**, *33*, 7377.
28. Luzzio, M. J.; Besterman, J. M.; Emerson, D. L.; Evans, M. G.; Lackey, K.; Leitner, P. L.; McIntyre, G.; Morton, B.; Myers, P. L.; Peel, M.; Sisco, J. M.; Sternbach, D. D.; Tong, W.-Q.; Truesdale, A.; Uehling, D. E.; Vuong, A.; Yates, J. *J. Med. Chem.* **1995**, *38*, 395.
29. Curran, D. P.; Jasperse, C. P.; Totleben, M. J. *J. Org. Chem.* **1991**, *56*, 7169.
30. Tanner, D. D.; Singh, H. K. *J. Org. Chem.* **1986**, *51*, 5182.
31. a) Volkmann, R. A.; Danishefsky, S.; Eggler, J.; Soloman, D. M. *J. Am. Chem. Soc.* **1971**, *93*, 5576. b) Volkmann, R. A., Ph.D. Thesis, University of Pittsburgh, 1972. c) S. Danishefsky, R. Volkmann, *Tetrahedron Lett.* **1973**, 2521.
32. Schultz, A. G. *Chem. Rev.* **1973**, *73*, 385.
33. Recent synthetic work: a) Comins, D. L.; Baevsky, M. F.; Hong, H. *J. Am. Chem. Soc.* **1992**, *114*, 10971. b) Shen W.; Coburn, C. A.; Bornmann, W. G.; Danishefsky, S. J. *J Org Chem* **1993**, *58*, 611. c) Comins, D. L.; Hong, H.; Jianhua, G. *Tetrahedron Lett.* **1994**, *35*, 5331. d) Comins, D. L.; Hong, H.; Saha, J. K.; Jianhua, G. *J. Org. Chem.* **1994**, *59*, 5120. e) Fang, F. G.; Xie, S.; Lowery, M. W. *J. Org. Chem.* **1994**, *59*, 6142. f) Rao, A. V. R.; Yadav, J. S.; Muralikrishna, V. *Tetrahedron Lett.* **1994**, *35*, 3613. g) Jew, S.-S.; Ok, K.-D.; Kim, H.-J.; Kim, M. G.; Kim, J. M.; Hah, J. M.; Cho, Y.-S. *Tetrahedron: Asymmetry* **1995**, *6*, 1245.
34. Simchen, G. *Chem. Ber.* **1970**, *103*, 389.
35. This impurity was carried through to the radical annulation. The experiments with the chloride analog of **13a** suggest that this does not participate to a significant extent in this reaction, and any remaining traces are removed by purification of the tetracycle.
36. Yaegashi, T.; Sawada, S.; Nagata, H.; Furuta, T.; Yokokura, T.; Miyasaka, T. *Chem Pharm. Bull.* **1994**, *42*, 2518.
37. Gokel, G. W.; Widera, R. P.; Weber, W. P. *Organic Syntheses*; Noland, W. E., Ed.; John Wiley and Sons: New York, 1988; Collect. Vol. 6, p 232.
38. Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, 633.
39. Ochiai, M.; Ito, T.; Takaoka, Y.; Masaki, Y. *J. Am. Chem. Soc.* **1991**, *113*, 1319.

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