titration. Aliquots (50 mL) of this solution were diluted with glass-distilled water (75 mL) to give stock solutions of NaOCl (0.4 M, 125 mL) which were saturated with NaCl (ca. 60 g) and filtered before use as described below.

2-Pyridone was purified by distillation (bp 130 °C (2.5 mmHg)) as was 4-pyridone (bp 130 °C (0.25 mmHg)).

Optimization of *N*-Chloropyridone Formation. The pyridone (2.5 mmol) in CH_2Cl_2 (25 mL) was shaken with the stock NaOCl solution (30 mL, 0.4 M) for a known time after which the organic layer was separated and dried by passing through a 10-cm column of anhydrous K_2CO_3. An aliquot (5 mL) was added to a solution of KI (2 g) in EtOH/AcOH (50:50, v/v, 20 mL) and the resultant mixture was titrated with standard sodium thiosulfate solution (0.01 N).

Time of *N*-Chloro to *C*-Chloro Rearrangement. The pyridone (10 mmol) in CH_2Cl_2 (100 mL) was shaken with a NaOCl solution (120 mL, 0.4 M) for the time previously determined as optimum for *N*-chloro formation. Then as above, the organic layer was separated and dried, and the *N*-chloropyridone content of aliquots (5 mL) was iodometrically determined at known time intervals until maximum conversion had occurred.

5-Chloro-2-pyridone. 2-Pyridone (4 g, 0.042 mol) in CH_2Cl_2 (400 mL) was shaken for 30 s with NaOCl solution (0.4 M, 520 mL, 0.21 mol) and saturated with NaCl. The organic layer was separated, dried with anhydrous K_2CO_3, and left standing for 24 h. The solvent was evaporated in vacuo and the resulting 5-chloro-2-pyridone (**3**) was recrystallized from C_6H_6 as needles (3.2 g, 59%), mp 163 °C (lit.[1] mp 163–165 °C).

3,5-Dichloro-2-pyridone. 5-Chloro-2-pyridone (0.5 g, 3.9 mmol) in CH_2Cl_2 (50 mL) was shaken for 1 min with a stock NaOCl solution (0.4 M, 60 mL, 24 mmol). The organic layer was separated, dried with anhydrous K_2CO_3, and left standing for 24 h. Evaporation of the solvent in vacuo gave the crude (0.39 g) product, which yielded 3,5-dichloro-2-pyridone (**5**) (0.25 g, 39%), mp 172 °C (lit.[1] mp 170–173 °C), as needles from C_6H_6.

1,3,5-Trichloro-2-pyridone. 3,5-Dichloro-2-pyridone (0.16 g, 1 mmol) in CH_2Cl_2 (16 mL) was shaken for 2 min with stock NaOCl solution (0.4 M, 20 mL, 8 mmol). The organic layer was separated and dried by passing though a 10-cm column of anhydrous K_2CO_3. The solvent was evaporated in vacuo at room temperature and the residue was immediately taken up into $CDCl_3$ (ca. 2 mL) for spectral analysis (Tables I–III). An aliquot (5 mL) of the organic layer before evaporation liberated I_2 from KI solution as described in the optimization procedure. The samples in $CDCl_3$ or $CHCl_3$, kept at 0 °C, remained stable (by ^1H NMR and iodometric titration) for at least a week.

3,5-Dichloro-4-pyridone. 4-Pyridone (0.6 g, 6.3 mmol) in $CHCl_3$ (100 mL) was shaken for 30 s with stock NaOCl solution (0.4 M, 120 mL, 48 mmol). The aqueous layer was separated and left standing overnight. A white precipitate of **9** formed which was filtered off, dried, and recrystallized from water as needles (1.0 g, 97%): mp >340 °C (lit.[18] mp >322–325 °C); *m/e* 167 (M + 4, 10.2%), 165 (M + 2, 62.0%), 163 (M, 100%), 162 (M − 1), 128 (M − 35) (loss of Cl atom), M − 70 (loss of 2Cl atoms).

1,3-Dichloro-4-pyridone. 4-Pyridone (0.476 g, 5 mmol), $CHCl_3$ (200 mL), $Ca(ClO)_2$ (1.9 g, 13 mmol), and H_2O (1 mL) were stirred at 20 °C for 4 h. The organic layer was separated and dried (K_2CO_3), and its 1,3-dichloro-4-pyridone content (8.2%) was determined iodometrically.

1,3,5-Trichloro-4-pyridone. 3,5-Dichloro-4-pyridone (0.330 g, 2.0 mmol) in $CHCl_3$ (200 mL) was shaken for 20 min with aqueous NaOCl (0.4 M, 25 mL, 10.0 mmol). The organic layer was separated and the aqueous layer repeatedly extracted with chloroform (100 mL, 50 mL, 40 mL). The chloroform extracts were mixed and dried (anhydrous K_2CO_3). 1,3,5-Trichloro-4-pyridone content was determined iodometrically (71%).

Acknowledgment. We thank Dr. M. Lopez-Rodriguez for ^{13}C spectra and PCSIR Labs Lahore (Pakistan) for a leave of absence (to G.R.K.).

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The Preparation of 2(1*H*)-Pyridinones and 2,3-Dihydro-5(1*H*)-indolizinones via Transition Metal Mediated Cocyclization of Alkynes and Isocyanates. A Novel Construction of the Antitumor Agent Camptothecin

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The intermolecular cocyclization of two alkynes with an isocyanate was examined utilizing (η^5-cyclopentadienyl)cobalt dicarbonyl [$CpCo(CO)_2$] and bis(η^4-1,5-cyclooctadiene)nickel [$(COD)_2Ni$] as catalysts. It was found that these compounds produced different amounts of 2-pyridone regioisomers. $CpCo(CO)_2$ also effectively catalyzes the cocyclization of 5-isocyanatoalkynes with monoalkynes to give 2,3-dihydro-5(1*H*)-indolizinones. The use of trimethylsilyl substituents ensures regioselectivity and allows the further elaboration of the 6-position to bear halo, alkenyl, and alkynyl substituents. This strategy is applied to synthetic approaches to the antitumor alkaloid camptothecin.

Structures containing the 2(1*H*)-pyridinone (2-pyridone) skeleton are rapidly gaining importance in synthetic and natural products chemistry. Compounds incorporating this nucleus are quite versatile as synthetic intermediates.[1] For example, treatment of 2-pyridones with phosphorus pentachloride generates 2-chloropyridines. The pyridone nucleus can be partially reduced via catalytic hydrogenation to piperidinones or further reduced to fully saturated piperidines.[1] Electrophilic substitution reactions with halogens occur often under mild conditions, furnishing products substituted in the 3- and 5-positions.[2] Nitration is also possible, yielding 3- or 5-nitro- and 3,5-dinitro-2-pyridones. The diene portion of the molecule can undergo Diels–Alder cycloaddition reactions with dienophiles,[3] or one double bond may act as a dienophile to an added

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(2) (a) Abramovitch, R. A.; Saha, J. G. *Adv. Heterocycl. Chem.* **1966**, *6*, 229. (b) Tee, O. S.; Paventi, M. *J. Am. Chem. Soc.* **1982**, *104*, 4142.

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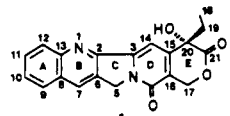
0022-3263/84/1949-4786$01.50/0

diene.[4] Some monocyclic pyridones are important medicinally since they exhibit antiinflammatory activity.[5]

Among the naturally occurring substances which incorporate the 2(1*H*)-pyridinone nucleus are ricinine,[6] fredericamycin A,[7] and tenellin.[8] Additional members of this class belong to the Lupinane group of alkaloids,[9] such as cytisine and anagyrine.

Interest in preparing structures containing the 2,3-dihydro-5(1*H*)-indolizinone skeleton developed almost exclusively as a result of the isolation and subsequent biological testing of the antitumor agent camptothecin (**1**).[10] Camptothecin has been isolated from *Camptotheca acuminata* Decne (Nyssaceae), a tree widely distributed in the southern part of China. It is also found in *Nothapodytes foetida* (Icacinaceae) along with a related alkaloid, mappicine (**2**).[10a] Camptothecin is antileukemic and has a certain therapeutic effect against gastric, rectum, colonic, and bladder tumors but is rather toxic to humans. Some camptothecin ring A analogues, such as 10-hydroxy- and 12-chlorocamptothecin exhibit lower toxicity and a broader antitumor spectrum in animals than the parent compound. Today the 10-hydroxy derivative is used in the clinical treatment of cancer in the People's Republic of China with success against liver carcinoma and tumors of the head and neck. The synthetic interest expressed in camptothecin since its isolation in 1966 is understandable in view of its unique heterocyclic ring system and its pronounced biological activity. There is a need for the development of synthetic routes to camptothecin due to the scarcity of the natural source, and to its analogues[11] for further biological evaluation.



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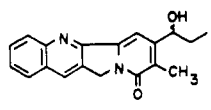


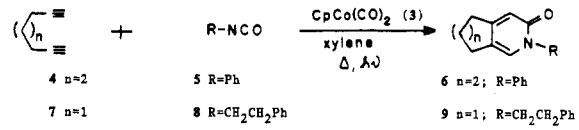
2

Recent interest in the 2-pyridone ring system has produced a number of new procedures for its preparation.[12] A novel and potentially general approach is the transition metal-catalyzed [2 + 2 + 2] cocyclization of two alkynes with an isocyanate.[13] This methodology has been examined independently by Hoberg[13a,b,24] and Yamazaki,[13c,d] but the synthetic utility of this transformation remains unexplored. The present report aims to fill this void by describing the potential of cobalt-catalyzed cocyclizations of isocyanates and alkynes in synthesis, including three formal syntheses of **1**.[14]

Table I. Calculated and Observed ^{13}C NMR Chemical Shifts in 2-Pyridones

		C-3	C-4	C-5	C-6
N-methyl-2-pyridone	obsd	119.1	139.5	104.8	139.5
12	calcd	131.2	150.4	116.8	148.4
	obsd	131.9	150.6	119.3	143.1
13	calcd	129.1	152.5	117.8	149.5
	obsd	130.9	152.2	119.4	145.1
14	calcd	130.1	149.4	114.7	150.5
	obsd	~130	146.8	120.7	152.0
15	calcd	128.0	151.5	115.7	151.6
	not obsd				

Cocyclization Reactions of Alkynes and Isocyanates Catalyzed by Cobalt and Nickel Compounds. When phenyl isocyanate (**5**) was allowed to react with 1,7-octadiyne (**4**) in the presence of $CpCo(CO)_2$ (**3**, 15 mol%) under conditions amenable to cocyclization,[15,21] the expected product, isoquinolone **6**, was isolated in 16% yield after chromatography. Variations in the reaction time, temperature, or substrate concentration did not improve this yield. Presumably, the balance of the isocyanate underwent competing side reactions (dimerization, trimerization, polymerization) under the reaction conditions,[16] although these products were never isolated. Consistent with this notion, an isocyanate less prone to self-condensation, β-phenethyl isocyanate (**8**),[17] reacted with 1,6-heptadiyne (**7**) to give **9** in somewhat improved yield (31%).



CpCo(COD) has been reported to be a catalyst in reactions of the type described above.[21d] However, use of this compound in the cyclization of **7** and **8** produced pyridone **9** in only 16% yield from a reaction mixture which was much more difficult to purify than the one obtained in the presence of **3**. Interestingly, when this cocyclization was attempted with bis(η^4-1,5-cyclooctadiene)nickel [**10**, $(COD)_2Ni$] as the catalyst,[13a,b] *no* pyridones were formed. The predominant products appeared to result from oligomerization of the diyne, as indicated by the abundance of signals in the aliphatic and olefinic regions in the ^1H NMR spectrum of the crude reaction mixture.

Complex **10** does, however, effectively catalyze the cocyclization of 1-phenyl-1-butyne (**11**) with β-phenethyl isocyanate (**8**). Of the four possible regioisomeric products which can result from this transformation, isomer **12** was

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(9) For general references see: Pelletier, S. W. "Chemistry of the Alkaloids"; Van Nostrand-Reinhold: New York, 1970. Glasby, J. S. "Encyclopedia of the Alkaloids"; Plenum Press: New York, 1975; Vol. 1 and 2. Coffey, S., Ed. "Rodd's Chemistry of Carbon Compounds", 2nd. ed.; Elsevier: Amsterdam, 1978; Vol. 4G and 4H. "The Alkaloids"; Specialist Reports; The Royal Society of Chemistry: London, 1969–1982; Vol. 1–12. "The Alkaloids"; Academic Press: New York, 1950–1983; Vol. 1–21.
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(15) Brien, D. J. M.S. Thesis, University of California—Berkeley, 1981.
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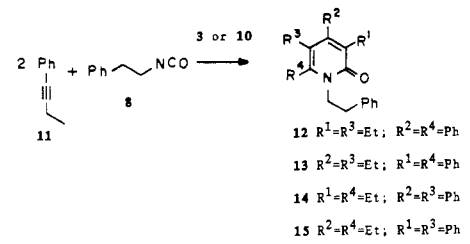
(17) Forster, M. O.; Stotter, H. *J. Chem. Soc.* **1911**, *99*, 1337.

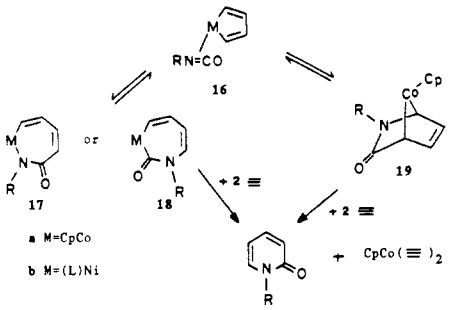


formed exclusively in 46% yield. This compound has the same substitution pattern as the product obtained by Hoberg in the analogous cocyclization of 1-phenyl-1-propyne and phenyl isocyanate.[13b] Hoberg assigned the regiochemistry of his compound based on an unpublished ^{13}C NMR spectrum. The carbon spectrum of **12** was consistent with the proposed substitution pattern (see below). Cocyclization of **11** and **8** mediated by $CpCo(CO)_2$ (**3**), however, produced a completely different product distribution. In this instance, the major isomer formed was pyridone **13** (47%), a regiochemical outcome consistent with results obtained by Yamazaki.[13c] Regioisomers **12** (16%) and **14** (13%) were obtained in minor amounts, while isomer **15** was not present in the reaction mixture.

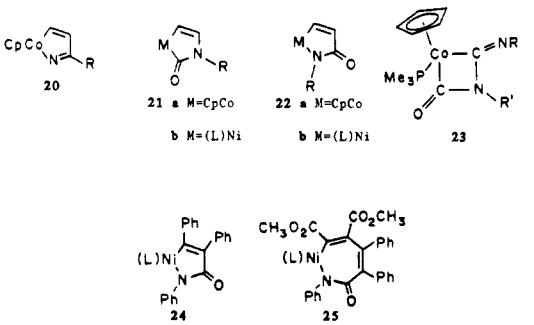
The assignment of these structures was not trivial and deserves comment. The chemical shifts of the ethyl groups in the ^1H NMR spectra of these compounds were very different (see Experimental Section), but not diagnostic. Comparison of the ^{13}C NMR spectra (^1H broad-band decoupled) allowed crude assignment of the isomers by adding substituent corrections[18c] for the ethyl and phenyl groups to the chemical shifts of the carbons in the unsubstituted 2-pyridone nucleus[18a] (see Table I). In addition, by obtaining non-^1H-decoupled ^{13}C NMR spectra it was possible to recognize pyridone carbons bearing similar substituents. The signals which corresponded to pyridone carbons attached to an ethyl group were multiplets, whereas carbons substituted by phenyl groups gave broad singlets. Based on the ^{13}C NMR data, there was only one isomer which would fit each set of coupled and decoupled spectra. The spectra, along with our assignments, are described in the Experimental Section. Clearly, there must be mechanistic differences between the cobalt- and nickel-catalyzed reactions to account for this remarkable difference in product selectivity.

Mechanistic Considerations: Comparison of Cobalt- and Nickel-Catalyzed Cocyclizations. Previous mechanistic investigations involving cobalt-catalyzed carbocycle[19,20] and pyridine[21c,d] formation provide a suitable

Scheme I



background within which to view the analogous reaction to prepare 2-pyridones. The cocyclization of isocyanates and alkynes catalyzed by $CpCoL_2$ [L_2 = $(CO)_2$, $(PPh_3)_2$, COD] is believed to adhere to the same catalytic cycle postulated for the cooligomerization of alkynes with nitriles (Scheme I, alkyne substituents omitted for clarity). Oxidative coupling of an intermediate bis(alkyne) complex, accompanied by complexation of the isocyanate generates key metalacycle intermediate **16a**. The isocyanate may add either via an insertion mechanism to give **17a** or **18a**, or via a Diels–Alder mechanism to produce bicyclic compound **19**. Either of these compounds can then undergo reductive elimination to give the 2-pyridone product plus the CpCo unit, which immediately complexes two more alkynes to reenter the catalytic cycle as a bis(alkyne) complex. Experimental evidence in the cobalt-catalyzed cyclization reaction of alkynes and nitriles indicates that metalacycle **20** is an unlikely intermediate in this pro-



cess.[21c,d] However, the intermediacy of metalacycles **21a**, **22a**, and others in the analogous reaction with isocyanates cannot be rigorously ruled out. The isolation of a compound of the type **23** by Werner[22] indicates that cobaltacycles such as **18a** and **21a** are not unreasonable intermediates in the catalytic cycle.

The regioisomeric distribution we obtained from the cocyclization of β-phenethyl isocyanate and 1-phenyl-1-butyne with $CpCo(CO)_2$ is in accord with a recent experimental–theoretical study carried out by Wakatsuki and Yamazaki in an attempt to explain the regioselectivity they observed in cobaltacycle formation from unsymmetrical alkynes.[23] Their calculations indicate that the regioisomeric distribution in the (irreversible) oxidative coupling of unsymmetrical alkynes depends primarily upon the steric requirements of the substituents, the more bulky group preferentially occupying the position α to cobalt.

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Hoberg proposed a different mechanism for the cocyclization of alkynes and isocyanates using $(COD)_2Ni$ as the catalyst and provides good, but not rigorous, experimental data to support it.[13a,24] His catalytic cycle involves **22b** as the key intermediate, capable of inserting another alkyne into the nickel–carbon bond to generate seven-membered metalacycle **17b**. Reductive elimination of this species would yield the pyridone product and a coordinatively unsaturated nickel complex which would reenter the catalytic cycle. Support for this mechanism is found by the isolation of a triphenyl-substituted intermediate **24** (L = TMEDA) and of metalacycle **25**, formed from the subsequent reaction of **24** with dimethyl acetylenedicarboxylate.[24] These findings do not preclude the possibility that nickelacycle **16b** is the true intermediate in the catalytic cycle, which could be formed through retrocyclization of **22b** and compounds of the type **25**, followed by complexation of more alkyne and subsequent oxidative coupling. Such a process, although not rigorously ruled out, appears unlikely in view of Hoberg's experimental results.

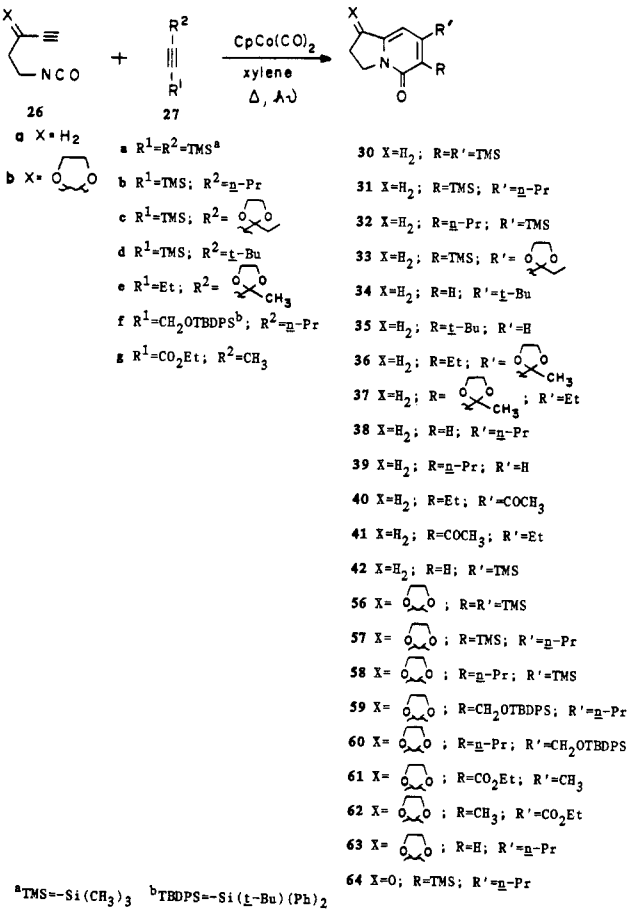
The regiochemical distribution of products in the nickel-catalyzed reaction follows Hoberg's mechanistic hypothesis, placing the larger substituents α to the nickel atom in the five- and seven-membered rings.[13a] This is reasonable based on steric grounds (as in the cobalt case) and agrees with the results we obtained for the $(COD)_2Ni$-catalyzed cyclization of β-phenethyl isocyanate and 1-phenyl-1-butyne.

When the cocyclization of β-phenethyl isocyanate and 1,7-octadiyne with $(COD)_2Ni$ was attempted, the products seemed to result from the polymerization of the diyne (see above). Examination of Hoberg's results reveals that cocyclizations involving terminal alkynes resulted in low yields of pyridone product.[13b] Although not stated explicitly in their work, this result may be due to nickel-mediated polymerization of the alkyne.[25]

The above studies are indicative of different reaction pathways available to cobalt and nickel catalysts. Synthetically, such differences may be of advantage, since these catalysts may complement each other when the preparation of a variety of substituted pyridones is desired. We next sought to investigate the metal-mediated cocyclization of α,ω-isocyanatoalkynes with monoalkynes. We hoped that the partial intramolecularity of this reaction would improve the yield of the cyclization, and perhaps give better regiochemical control over the product distribution.

Cobalt-Catalyzed Cocyclizations of 5-Isocyanatopentynes with Monoalkynes. Model Studies with 5-Isocyanatopentyne. The eventual goal of this investigation was to find new routes to the alkaloid camptothecin (**1**). Thus, we chose to investigate the cocyclization of 5-isocyanatopentyne (**26a**) with disubstituted alkynes (**27**) by using $CpCo(CO)_2$ (**3**) as the catalyst. The products of this reaction would be 2,3-dihydro-5(1*H*)-indolizinones, bicyclic compounds with a nitrogen atom at the bridgehead position (Scheme II). Of particular interest was the regiochemical distribution of the products, as regioselectivity is desirable if the process is to be important synthetically. It was known from previous studies involving the cyclization of 6-heptynenitrile with unsymmetrical disubstituted alkynes that the larger alkyne substituent tended to end up α to the nitrogen atom in the pyridine product, particularly if it was a trimethylsilyl group.[21b] We expected the same substitution pattern in the cyclizations with isocyanatopentynes, based on the proposed mechanism involving analogous metalacycles.

Scheme II



The required 5-isocyanatopentyne (**26a**) was prepared by the conversion of the known[26] 5-hexynoic acid **28** to the acid chloride **29** using oxalyl chloride in benzene,[27] followed by treatment of the acid chloride with sodium azide in dry acetonitrile at reflux.[28] Alkynes **27a**, **27b**, and **27d** (for compound structures see Scheme II) were prepared by using literature procedures.[29] Compounds **27c** and **27e** were synthesized by ketalization of the known[30c] 1-(trimethylsilyl)-1-pentyne-3-one and the commercially available[31] 3-hexyne-5-one under standard conditions (ethylene glycol, *p*-toluenesulfonic acid, benzene, reflux).

A number of disubstituted alkynes were cocyclized with **26a** to examine the generality and regioselectivity of the reaction. Typically the isocyanate (1 equiv) in *m*-xylene and the alkyne (3–5 equiv.) along with $CpCo(CO)_2$ (0.2 equiv) in *m*-xylene were added with two separate syringes via syringe pump (3–5 h) to boiling and irradiated (visible ligh) *m*-xylene. An exception to this procedure involved

(24) Hoberg, H.; Oster, B. W. *J. Organomet. Chem.* **1983**, *252*, 359.
(25) For examples of nickel-catalyzed polymerizations, see: (a) Jolly, P. W.; Wilke, G. "The Organic Chemistry of Nickel"; Academic Press: New York, 1975; Vol. 2. (b) Meriwether, L. S.; Colthup, E. C.; Kennerley, G. W.; Reusch, R. N. *J. Org. Chem.* **1961**, *26*, 5155. (c) Meriwether, L. S.; Colthup, E. C.; Kennerley, G. W. *Ibid.* **1961**, *26*, 5163. (d) Colthup, E. C.; Meriwether, L. S. *Ibid.* **1961**, *26*, 5169.
(26) Eglinton, G.; Whiting, M. C. *J. Chem. Soc.* **1953**, 3052.
(27) Shamma, M.; Smithers, D. A.; St. Georgiev, V. *Tetrahedron* **1973**, *29*, 1949.
(28) For a review of the Curtius rearrangement, see: Smith, P. A. S. *Org. React.* **1946**, *3*, 337.
(29) Brandsma, L. "Preparative Acetylenic Chemistry"; Elsevier: New York, 1971. (b) Brandsma, L.; Verkruijsse, H. D. "Synthesis of Acetylenes, Allenes and Cumulenes"; Elsevier: Amsterdam, 1981.
(30) (a) Newman, H. *J. Org. Chem.* **1973**, *38*, 2254. (b) Walton, D. R. M.; Waugh, F. *J. Organomet. Chem.* **1972**, *37*, 45. (c) Birkofer, L.; Ritter, A.; Uhlenbrauch, H. *Chem. Ber.* **1963**, *96*, 3280.
(31) Purchased from Farchan Acetylenes, Story Chemical Co.

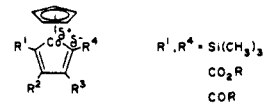
Table II. Results of the Cocyclization of 26 with Alkynes

entry	isocyanatoalkyne	alkyne	products (%)
1	**26a**	**27a**[b]	**30** (72)
2	**26a**	**27b**	**31** (68), **32** (5)
3	**26a**	**27c**	**33** (76)
4	**26a**	**27d**	**34**[a] (17), **35** (<1)
5	**26a**	**27e**	**36** (41), **37** (31)
6	**26b**	**27a**[b]	**56** (68)
7	**26b**	**27b**[c]	**57** (60), **58** (3)
8	**26b**	**27f**	**59** (20), **60** (18)
9	**26b**	**27g**	**61** (14), **62** (17)

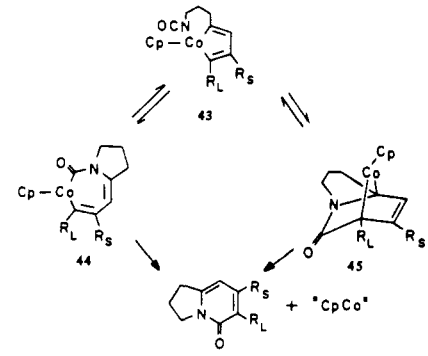
[a] Products were isolated in their protodesilylated form after chromatography on silica. [b] Alkyne **27a** used as solvent. [c] Alkyne **27b** used as solvent.

bis(trimethylsilyl)ethyne (**27a**) which was used as the solvent. After an additional $^1/_2$ of heating and irradiation, the solvent was removed by vacuum transfer and the products were purified by chromatography on silica. The results are summarized in Table II. The regiochemical assignments of **31** and **32** (entry 2) were based on comparison of the ^{1}H NMR spectra of the protodesilylated analogues (**38**, **39**) with known compounds.[32] The desilylation procedures [CF_3CO_2H, C_6H_6 or $(CH_3)_4N^+F^-\cdot 3H_2O$, Me_2SO, 1 h, 60–80 °C] are those also applied to silylbenzenes[19] and silylpyridines.[15,21c] The chemical shifts and coupling constants of the pyridone protons are very distinctive and clearly indicate whether a 6,8- or a 7,8-disubstituted indolizinone is present. Regiochemical assignments of **36** and **37** (entry 5) were made by comparison of the ^{1}H coupled and uncoupled ^{13}C NMR spectra of their corresponding regioisomeric ketones with values calculated by using substituent effect corrections[18c] on the chemical shifts of the parent 2-pyridone nucleus. The most diagnostic signal was that of the C-9 pyridone carbon in the hydrolyzed products. Ketone isomer **40** showed a C-9 peak at δ 147.4, while ketone **41** exhibited a peak which was much further downfield (δ 156.5), indicative of an acetyl group in the 6-position (*p*-position to C-9). These assignments correlated well with values reported in the literature for similar structures.[18a,b] Compound **34** was isolated in its protodesilylated form after chromatography on silica.

One notes that good chemo- and stereoselectivity was achieved when trimethylsilylated alkynes were employed in the cyclization, the silyl group emerging preferentially α to the amide linkage, even when pitted against *tert*-butyl (entry 4). This effect, if steric in origin, is puzzling, because the experimental *A* values for trimethylsilyl and *tert*-butyl are 2.4–2.6 and >4.5 kcal/mol, respectively.[33a] This finding would stipulate that the *tert*-butyl group, being much larger, at least in the cyclohexane ring flip,[33b] would prefer an orientation α to the metal, *contrary* to our experimental results. It may be possible that *A* values are not applicable to this system. Indeed, Yamazaki has found good correlation between the regiochemical orientation of the substituents and their cone angles,[23] and the trimethylsilyl group might well be larger in this respect than *tert*-butyl.[33c] There could also be an electronic effect associated with silicon. Theoretical calculations by Wakatsuki and Yamazaki[23] indicate that the cobalt–carbon bond of the metalacycle intermediate is polarized as shown below. This being the case, it follows that electron-withdrawing groups (trimethylsilyl,[34] ester, ketone) in the 2- and 5-positions (R^1 and R^4) would stabilize this intermediate. This orientation is also favored kinetically, according to molecular orbital calculations by Hoffmann.[35]



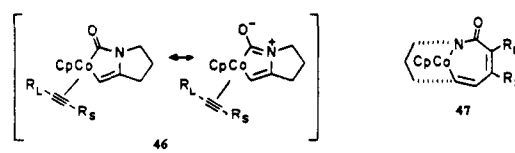
Scheme III



Considering both electronic and steric contributions of the substituents, and assuming a cobaltacyclopentadiene intermediate, a catalytic cycle for this reaction can be postulated (Scheme III) based on previously hypothesized cobalt-catalyzed cooligomerization mechanisms.[21] Addition of the isocyanate unit to the metalacycle in **43** via insertion (to give **44**) or Diels–Alder cycloaddition (to form **45**) followed by reductive elimination would result in the pyridone product in which the larger group is located α to the pyridone carbonyl and a coordinatively unsaturated cobalt species which is ready to reenter the catalytic cycle.

There are fewer mechanistic alternatives to this reaction than the intermolecular cyclizations discussed earlier. One could invoke complex **46** as the precursor to **44**, provided that subsequent insertion of the alkyne occurred into the vinylcobalt–carbon bond. Such a mechanism would be similar to Hoberg's nickel-catalyzed pyridone synthesis.[13a,24] Diels–Alder cycloaddition of the alkyne in metalacycle **46** would seem unlikely.

Regioisomeric insertion of the isocyanate group in **43** would lead to the intermediacy of cobaltacycle **47**, unreasonable due to the strain involved in the formation of such a compound. All factors considered, we believe that the most likely mechanism is as depicted in Scheme III. After the generality and regioselective preferences of the cobalt-catalyzed cocyclization reaction of alkynes with 5-isocyanatopentyne were established, the method was extended to develop new approaches to camptothecin (**1**).

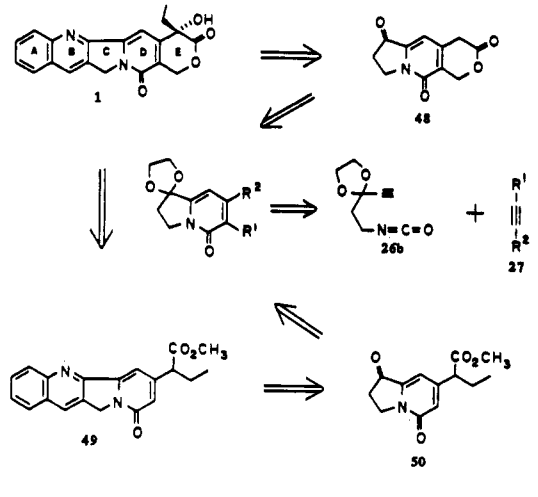


Preparation of Protected 2,3-Dihydro-1,5-indolizinediones via Cobalt-Catalyzed Cyclizations. Synthetic Strategies toward Camptothecin. A retrosynthetic analysis of camptothecin based on the cobalt-catalyzed cyclization of derivatized 5-isocyanatopentynes with monoalkynes is outlined in Scheme IV. The upper

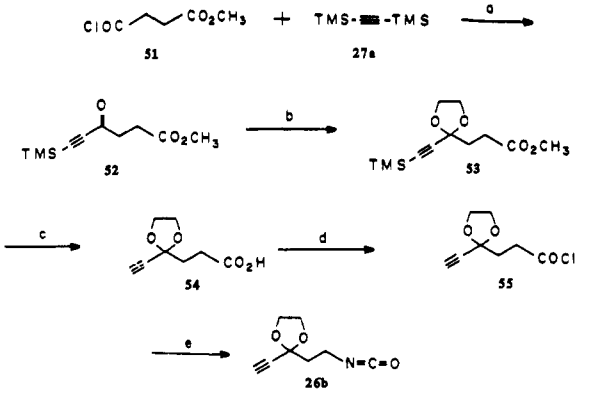
(32) Fujii, T.; Ohba, M.; Hiraga, T. *Heterocycles* **1981**, *16*, 1197.
(33) (a) Kitching, W.; Olszowy, H. A.; Drew, G. M.; Adcock, W. *J. Org. Chem.* **1982**, *47*, 5153. (b) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 5023. (c) Cone angles: H, 75; Me, 90; COMe, 100; CO_2Me, ~100; *i*-Pr, 114; *t*-Bu, 126; Cp, 136: Tolman, C. A. *Chem. Rev.* **197**, 77, 313. (d) Eliel, E. L. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 761.

(34) Corresponding σ_I and σ_R values for substituents: CO_2Et, 0.34, 0.11; $Si(CH_3)_3$, –0.13, 0.09; *t*-Bu, –0.07, –0.13. Charton, M. *Chemtech* **1974**, 502; **1975**, 245.
(35) Stockis, A.; Hoffmann, R. *J. Am. Chem. Soc.* **1980**, *102*, 2952.

Scheme IV



Scheme V[a]



[a] (a) $AlCl_3$, CH_2Cl_2, 0 °C, 83%, (b) $HOCH_2CH_2OH$, TsOH, C_6H_6, Δ, 97%; (c) NaOH, CH_3OH, H_2O, 83%; (d) $(COCl)_2$, C_6H_6, DMF (catalyst), 25–35 °C, 82%; (e) NaN_3, CH_3CN, Δ, 84%.

pathway (**48** → **1**) closes the E ring lactone at an early stage and annulates the A, B quinoline ring onto the ketone of **48** late in the synthesis. The lower approach (**50** → **49** → **1**) reverses the order of A, B, and E ring formation. Regardless of which strategy is eventually pursued, both key indolizinediones **48** and **50** must arise from a protected 2,3-dihydro-1,5-indolizinedione, the result of the regioselective cocyclization of monoalkyne **27** and isocyanate **26b**.

The required isocyanatoalkyne **26b** was prepared from 3-carbomethoxypropanoyl chloride (**51**)[36] according to Scheme V.

The indolizinones obtained from the cocyclization of **26b** and monoalkynes (Scheme II) are given in Table II. One notes the same regioselectivity in entry 7 that was observed with isocyanate **26a** and alkyne **27b** (entry 2). Indolizinone regioisomer **57** was identified by the ^1H NMR spectrum of its corresponding desilylated compound. Pyridone hydrogen resonances appeared at δ 6.11 and 6.35, with a coupling constant of 1.1 Hz, consistent with literature values for this substitution pattern.[32]

In an attempt to circumvent problems associated with the introduction of the hydroxymethyl group at the C-16 position of camptothecin,[10] protected propargylic alcohol **27f** was cocyclized with **26b** (entry 8) in the hope that the bulky *tert*-butyldiphenylsilyl group would influence regioselectivity. Unfortunately, a mixture of isomers was produced in about a 1 to 1 ratio. Apparently, the silyl group is too far removed from the reaction center to be a factor in influencing regioisomeric metalacycle formation. Steric or electronic differences between carbethoxy and methyl groups[15,33c,d] do not seem to be important in the reaction of **27g** with isocyanatoalkyne **26b** (entry 9) as a nearly 1 to 1 mixture of products was formed, albeit in low yield. Isomer **61** was shown to be identical with the compound prepared by Shammma in his formal synthesis of camptothecin.[27] Since good yields and regioselectivity were obtained only when the alkyne was substituted with a trimethylsilyl group, indolizinone **57** was chosen as an appropriate candidate for the further manipulation to camptothecin.

Elaboration of Indolizinones. Through utilization of the cobalt-catalyzed cocyclization of isocyanatoalkyne **26b** and 1-(trimethylsilyl)-1-pentyne, we accomplished a primary goal: to prepare a protected indolizinone with regiochemical control over the substituents in the 6- and 7-positions (Scheme II). What remained was to modify structure **27** to camptothecin (**1**). The 2-(1,3-dioxolane) group at position 1 could presumably be hydrolyzed to the ketone, suitable for Friedländer condensation, and was not expected to cause any difficulties in the synthesis. Formation of the E ring lactone, however, required formal hydroxymethylation at the 6-position and carboxylation and oxidation at the α-position of the 7-*n*-propyl group. It seemed that the key to the introduction of a carbon substituent at position 6 lay with the trimethylsilyl group. (Trimethylsilyl)pyridones are quite rare, having been reported in the literature only twice,[39] and subsequent transformations of these compounds were not known.

Vinylic and aromatic trialkylsilyl groups are well-known to undergo electrophilic substitution reactions, the products being the result of ipso substitution.[40] The silyl group is also susceptible to cleavage with fluoride ion. Since, as mentioned earlier, electrophilic attack of halogens on 2-pyridones occurs primarily at the 5-position and to a lesser extent, the 3-position (corresponding to the 8- and 6-positions of indolizinones),[1,2] it was of interest to establish to what extent the ipso-directing power of the trimethylsilyl group in our systems would override the intrinsic electronic properties of the pyridone ring in such a reaction.

We had observed earlier that cleavage of a 7-(trimethylsilyl)indolizinone required the use of fluoride ion (see above). It was therefore not surprising that bis(trimethylsilyl)indolizinone **30** could be selectively monodesilylated at the more nucleophilic 6-position. The ^1H NMR spectrum of **42** showed singlets at δ 6.52 and 6.14, attributed to the pyridone protons in this substitution pattern.[32] Treatment of **57** with trifluoroacetic acid under nonaqueous conditions produced **63** by protodesilylation, whereas treatment of **57** with aqueous hydrochloric acid gave the (trimethylsilyl)indolizinedione **64**.

Direct attack of a carbon electrophile at the silylated 6-position would provide a facile introduction of the hydroxymethyl group (or its precursor) required in camptothecin. It was known from Danishefsky's work that hydroxymethylation of nonsilylated pyridones of this type produced mixtures of isomers, electrophilic attack occurring at the 6- and 8-positions.[41] For the purpose of model

(36) Cason, J. In "Organic Syntheses"; Horning, E. C., Ed.; Wiley: New York, 1955; Collect. Vol. III, p 169.
(37) Warren, C. K.; Weedon, B. C. L. *J. Chem. Soc.* **1958**, 3972.
(38) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975.
(39) (a) Sakata, T.; Adachi, K.; Akahori, Y.; Hayashi, E. *Yakugaku Zasshi* **1967**, *87*, 1374; *Chem. Abstr.* **1968**, *68*, 59649. (b) Simchen, G.; Pfletschinger, J. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 428.
(40) Colvin, E. "Silicon in Organic Synthesis"; Butterworths: London, 1981.

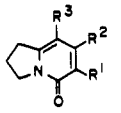
Table III. Iodination of (Trimethylsilyl)indolizinones with ICl

entry	substrate	product	% yield
1	**30**	**70**	90
2	**31**	**71**	66
3	**33**	**72**	94
4	**56**	**73**	86
5	**57**	**74**	93

studies, indolizinone **31** was used as the substrate. Attempts at direct hydroxymethylation under the conditions described by Danishefsky[41] (paraformaldehyde, dioxane, water, acid, Δ) led only to desilylated product. Sugasawa was able to formylate 4-methoxy-1-methyl-2-pyridone by using Vilsmeier's reagent (DMF, $POCl_3$) and had utilized this reaction in a synthesis of camptothecin.[42] However, again only desilylated compound was obtained when we attempted this reaction on **31**. It is known that (trimethylsilyl)alkenes can be formylated with 1,1-dichloromethyl methyl ether and titanium tetrachloride,[43] but when these reagents were added to **31**, no reaction took place, except for a small amount of desilylation. Apparently the Lewis acid complexes to the heteroatoms of the pyridone, greatly attenuating electrophilic attack on the nucleus.

A Mannich reaction might also result in the introduction of an electrophilic one-carbon unit.[44] Applying conditions which have been used previously in Mannich reactions with 3-pyridones[45] to **31** gave no reaction. Treatment of **31** with preformed dimethylmethyleneiminium chloride[46] produced indolizinone **65** in 33% yield, in which the electrophile had attacked the only open position on the ring, rather than ipso to the trimethylsilyl group. From these experiments it was concluded that it would not be possible to replace the 6-trimethylsilyl group with a carbon substituent by direct electrophilic attack. We therefore turned our attention to the utility of possible halogenations and the further elaboration of 6-halo derivatives to 6-alkylated systems en route to camptothecin.

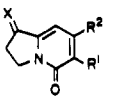
Usually, bromination of 2-pyridones is rapid and difficult to control. Mixtures of 5-bromo, 3-bromo-, and 3,5-dibromo-2-pyridones often result.[1,2] Iodination requires more forcing conditions, and selectivity is still a problem. We have found that bromination of 6-(trimethylsilyl)-indolizinones is also very rapid, and occurs with a high degree of selectivity for the 6-position. Treatment of **31** with 1 equiv of bromine in dichloromethane gave monobrominated product **66** in 73% yield. Addition of a second equiv of bromine produced the dibromo compound **67**. This result should be compared with the product distribution obtained when 1 equiv of bromine was added to the nonsilylated indolizinone **38**. The electrophilic substitution pattern characteristic of 2-pyridones is observed, in which



65 R^1=TMS; R^2=n-Pr; R^3=$CH_2N(CH_3)_2$
66 R^1=Br; R^2=n-Pr; R^3=H
67 R^1=R^3=Br; R^2=n-Pr
68 R^1=H; R^2=n-Pr; R^3=Br
69 R^1=Br; R^2=  ; R^3=H

the 8-bromo product **68** predominates (36%), along with smaller amounts of **66** and **67**. Bromination of ketalized indolizinone **33** to produce **69** without adversely affecting the ketal was possible in the presence of added pyridine.

Iodination of 6-(trimethylsilyl)indolizinones with iodine monochloride[47] gave good yields of monoiodoindolizinones. The results are summarized in Table III. Monoiodination occurred, even when bis(trimethylsilyl)indolizinone **56** was exposed to a 2-fold excess of ICl. Confirmation of the substitution pattern was obtained by converting the iodo compound **73** ultimately to desilylated indolizinone **80** (see below). The ^1H NMR spectrum of **80** clearly indicated hydrogens in the 6- and 7-positions. Furthermore, it was found that the addition of pyridine was not necessary to protect the ketal in the iodinations of **33**, **56**, and **57**.



70 X=H_2; R^1=I; R^2=TMS
71 X=H_2; R^1=I; R^2=n-Pr
72 X=H_2; R^1=I; R^2=
73 X=  ; R^1=I; R^2=TMS
74 X=  ; R^1=I; R^2=n-Pr
75 X=H_2; R^1= -C≡CPh; R^2=n-Pr
76 X=  ; R^1= -C≡CPh; R^2=n-Pr
77 X=  ; R^1=t-CH=$CHCO_2CH_3$; R^2=n-Pr
78 X=  ; R^1=t-CH=$CHCO_2CH_3$; R^2=TMS
79 X= ; R^1=t-CH=CHPh; R^2=TMS
80 X=  ; R^1=t-CH=CHPh; R^2=H

The halo group of the haloindolizinones obtained from the halogenation of the trimethylsilyl derivatives was envisioned to be convertible to carbon-containing substituents through transmetalation of the halopyridone, followed by trapping with an electrophilic carbon, or by coupling of an organometallic species with the halopyridone using a transition metal catalyst (Pd or Ni). However, the 6-haloindolizinones could not be transmetalated with *n*-butyllithium or *tert*-butyllithium,[48] nor could they be coupled with Grignard or lithium reagents using nickel or palladium catalysts.[49] Also unsuccessful was the attempted cyanation with KCN and a palladium catalyst[50] and the direct carboalkoxylation or formylation involving carbon monoxide and a catalyst.[51]

We were pleased to find that phenylacetylene coupled[52] with iodoindolizinones **71** and **74** in the presence of

(41) (a) Volkmann, R.; Danishefsky, S.; Eggler, J.; Solomon, D. M. *J. Am. Chem. Soc.* **1971**, *93*, 5576. (b) Danishefsky, S.; Volkmann, R. *Tetrahedron Lett.* **1973**, 2521. (c) Danishefsky, S.; Etheredge, S. J. *J. Org. Chem.* **1974**, *39*, 3430.

(42) Sugasawa, T.; Toyoda, T.; Sasakura, K. *Chem. Pharm. Bull.* **1974**, *22*, 771.

(43) (a) Yamamoto, K.; Nunokawa, O.; Tsuji, J. *Synthesis* **1977**, 721. (b) Yamamoto, K.; Yoshitake, J.; Qui, N. T.; Tsuji, J. *Chem. Lett.* **1978**, 859. (c) Yamamoto, K.; Ohta, M.; Tsuji, J. *Ibid.* **1979**, 713.

(44) There has been only one report describing a Mannich reaction with a 2-pyridone: Nakamura, A.; Kamiya, S. *Chem. Pharm. Bull.* **1968**, *16*, 1466.

(45) (a) Smirnov, L. D.; Lezina, V. P.; Bystrov, V. F.; Dyumaev, K. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1965**, 198; *Chem. Abstr.* **1965**, *62*, 11774d. (b) Smirnov, L. D.; Lezina, V. P.; Bystrov, V. F.; Dyumaev, K. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1965**, 1836; *Chem. Abstr.* **1966**, *64*, 5038c.

(46) (a) Kozikowski, A. P.; Ishida, H. *Heterocycles* **1980**, *14*, 55. (b) Kinast, G.; Tietze, L.-F. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 239.

(47) Félix, G.; Dunoguès, J.; Pisciotti, F.; Calas, R. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 488. Also see ref 19c.

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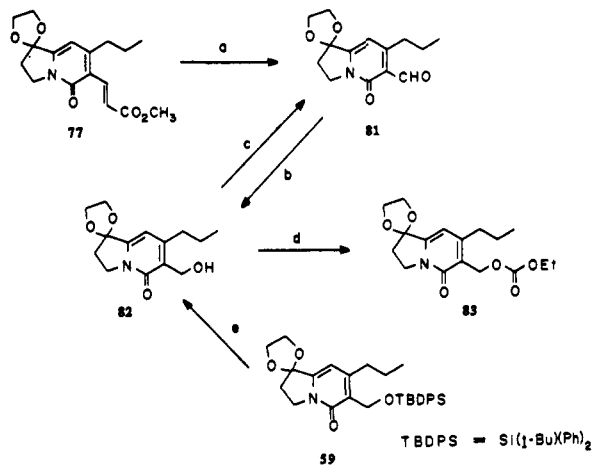
Scheme VI[a]



[a] (a) OsO_4, $NaIO_4$, ether, H_2O, 86 %; (b) $NaBH_4$, EtOH, 0 °C, 87%; (c) MnO_2, CH_2Cl_2, 94%; (d) $ClCO_2Et$, pyridine, 0 °C, 90%; (e) n-Bu_4NF, THF.

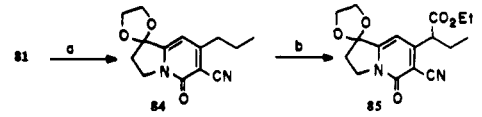
$PdCl_2(PhCN)_2$ to give 6-(phenylethynyl)indolizinones **75** and **76** in high yield. In addition, the same palladium-catalyzed vinylation reactions that produce styrenes[53] and vinylic pyrimidinones[52c] from their respective iodo-compounds also gave high yields of vinylated indolizinones **77** (97%) and **78** (93%) from their corresponding iodo-precursors and methyl acrylate. The analogous reaction using styrene produced the adduct **79** from **73**, which was desilylated with fluoride ion to give unsilylated derivative **80**, proving unequivocally the regiochemistry of the iodination reaction en route to **73**.

With respect to an approach to the total synthesis of camptothecin, the palladium-catalyzed coupling reaction of 6-iodoindolizinone **74** with methyl acrylate had solved the problem of introducing a carbon substituent at C-6. The vinylic unit now had to be converted into a hydroxymethyl group, and the α-position of the n-propyl chain carboxylated to produce the lactone which would eventually become the E ring of camptothecin.

Manipulation of Substituents. Formal Syntheses of Campthothecin. The double bond of the α,β-unsaturated ester side chain of compound **77** was readily cleaved with $OsO_4/NaIO_4$ to generate aldehyde **69** (Scheme VI).[54] The aldehyde singlet at δ 10.50 in its ^1H NMR spectrum correlates well with values reported for other 3-formyl-2-pyridones.[42] Reduction[55] of the aldehyde with sodium borohydride in ethanol furnished the alcohol **82**, which could be converted into the mixed carbonate **83** with ethyl chloroformate.[56] The alcohol **82** could also be reoxidized to the aldehyde **81** with manganese dioxide[57] under mild conditions. The structure of **59** was proven in this way by converting it into the alcohol **82** by desilylation, followed by oxidation to aldehyde **81**.

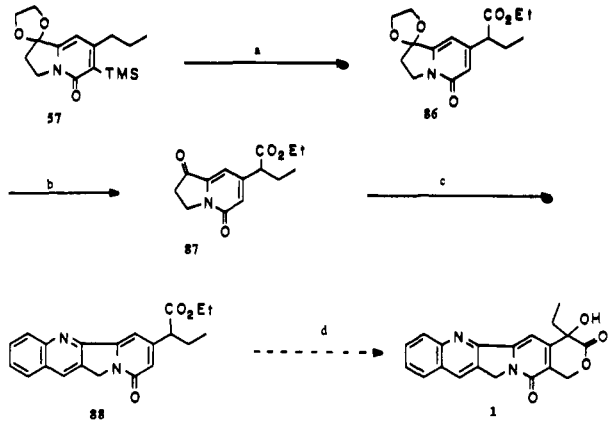
Attempts to cyclize carbonate **83** intramolecularly under the influence of base were not successful. A variety of bases were tried [LDA, $(Me_3Si)_2NLi$, t-BuLi, KH, NaOEt, NaH] with various solvents and conditions, but the starting material would either hydrolyze back to alcohol **82** or undergo decomposition.

Scheme VII[a]



[a] (a) $NH_2OH{\cdot}HCl$, SeO_2, 80%; (b) $(EtO)_2CO$, NaH, toluene, EtOH, 32%.

Scheme VIII[a]



[a] (a) $(CH_3CH_2O)_2CO$, KH, toluene, 54%; (b) $(COOH)_2$, CH_3CH_2OH, H_2O, 75%; (c) N-(2-aminobenzylidene)-p-toluidine, TsOH, toluene, 78%; (d) ref 41.

Attempts were made to carbethoxylate the α-carbon of the n-propyl side chain of several indolizinone derivatives. Carbethoxylation failed with indolizinones **77**, **81**, **82**, **83**, **59**, **75**, and **76** using the procedure described by Wall,[58] or modifications thereof.[59]

Inspection of the literature reveals that the only successful attempts at deprotonating the α-position of the alkyl side chain of a pyridone had been in cases in which the nucleus was substituted with one or more activating nitrile groups[58,59,60a,b] or an ester function.[27,60c] To facilitate carbethoxylation in our system, aldehyde **81** was converted into the cyanoindolizinone **84** according to the procedure described by Sosnovsky.[61] This compound underwent carbethoxylation utilizing the conditions reported by the Chinese group[59] to result in indolizinone **85** in modest yield (Scheme VII). This compound was identical (^1H NMR, IR, MS) with the intermediate prepared by these authors and Wall[58] in their respective syntheses of camptothecin. Comparison of yields shows that our procedure (11 steps, 6% yield from 3-carbomethoxypropanoyl chloride) is inferior to either of the former preparations, both starting from cyanoacetamide. Wall obtained **85** in 33% yield in six steps; the Chinese group prepared **85** in six steps in 28% yield.

Surprisingly, carbethoxylation also occurred when the seemingly unactivated indolizinone **57** was allowd to react with diethyl carbonate under the conditions described by Wall (Scheme VIII). Apparently the trimethylsilyl group increases the acidity of the hydrogens on the α-position of the propyl group, much like an ester.[34] This indicates yet another useful feature of our approach involving silyl-alkynes. The trimethylsilyl group was presumably cleaved

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via attack of ethoxide ion.[40] The product, indolizinone **86**, was deketalized with water and oxalic acid[27] and condensed with *N*-(2-aminobenzylidene)-*p*-toluidine[62] to give tetracyclic compound **88**, which intercepts Danishefsky's synthesis of camptothecin (**1**) and three other formal syntheses (as the methyl ester **49**, see Scheme IV). Compound **88** was made by us starting from 3-carbomethoxypropanoyl chloride in nine steps, 9% yield, superior to Danishefsky's route[41a] (11 steps, 1.2%) and Quick's synthesis[63] (10 steps, 9%) both from 3-aminopropanal dimethyl acetal and the Kende approach[64] from furfural dimethyl acetal (13 steps, 2.7%) but inferior to Büchi's strategy[65] from methyl 2,2-dimethoxyethanoate (six steps, 18%). The ethyl ester **88** could be quantitatively transesterified to the methyl ester **49** by exchange with sodium methoxide. This compound was identical with tetracycle **49** obtained by Danishefsky and Büchi.[66]

Summary

In this report we have shown that the cobalt-catalyzed cocyclization of α,ω-isocyanatoalkynes with monoalkynes is a uniquely versatile, convergent procedure for the preparation of a wide variety of annulated pyridones. High regioselectivity is achieved when (trimethylsilyl)alkynes are utilized as to cocyclization component. The (trimethylsilyl)pyridones thus obtained can be iodinated much more easily and with higher selectivity than their nonsilylated counterparts. Facile palladium-catalyzed ethynylation and vinylation of iodopyridones generate useful synthetic intermediates which can be converted into other derivatives by using traditional organic reactions. Finally, we have extended these techniques to synthesize known intermediates en route to camptothecin (**1**), a natural product exhibiting antitumor activity.

Experimental Section

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran (THF) was distilled from sodium–benzophenone immediately prior to use. All reactions involving organometallic reagents were conducted under a nitrogen atmosphere. Melting points were determined in open Pyrex capillary tubes on a Thomas-Hoover Unimelt apparatus and are uncorrected. IR spectra were recorded with a Perkin-Elmer Model 137 or a Perkin-Elmer Model 681 infrared recording spectrometer. ^{1}H NMR spectra were measured on a Varian EM 390 (90 MHz) or on home-built 200- and 250-MHz instruments, consisting of Cryomagnets Inc. magnets and Nicolet Model 1180 data collection systems, assembled by R. Nunlist (UC Berkeley). Spectra are reported in δ referenced to Me_4Si or, where indicated, measured relative to the residual solvent proton peak. Significant ^{1}H NMR data are tabulated in order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), number of protons, coupling constant(s) in Hertz, and assignment if possible and necessary. ^{13}C NMR spectra were measured at either 25.14 MHz on a Bruker spectrometer equipped with a Varian magnet and a Nicolet Corporation TT-23 Fourier Transformation Computer package, at 50.78 MHz on the UCB 200, or at 63.07 MHz on the UCB 250. The chemical shifts are reported in ppm downfield from Me_4Si, referenced to the central peak of the deuteriochloroform triplet (77.0 ppm). Mass spectra were obtained with Atlas MS-12 (low-resolution) and Consolidated 12-110B (high-resolution) mass spectrometers. Peak intensity is expressed as percent total ion current. Elemental analyses were provided by the Microanalytical Laboratory, operated by the College of Chemistry, University of California, Berkeley, CA. All liquid chromatography was carried out on EM Reagents silica gel 60 (70–230 mesh ASTM) unless otherwise specified. Thin-layer chromatography was done on commercial silica gel plates (Merck) PF-254 containing $CaSO_4$ and fluorescent indicator. Preparative TLC was performed by using plates prepared from EM reagents silica gel PF-254 with $CaSO_4{\cdot}^1/_2H_2O$. A spinning plate, continuous elution system (Chromatotron, Harrison Research) was used. Unless otherise specified, all solid products were recrystallized from dichloromethane/hexane.

Cobalt-Catalyzed Cocyclizations. General Procedure. The monoalkyne (1 equiv) was dissolved in *m*-xylene (15 mL) in a 50-mL round-bottom flask (pretreated with hexamethyldisilazane) equipped with a coil condenser. This mixture was degassed by using three freeze–pump–thaw cycles and brought to reflux (oil bath) under a nitrogen atmosphere. The isocyanate (1 equiv) and the monoalkyne (3–5 equiv) were dissolved in degassed *m*-xylene to a total volume of 5 mL and loaded into a 5-mL syringe. Into another 5-mL syringe was placed $CpCo(CO)_2$ (typically 0.15 equiv, density 1.42) in degassed *m*-xylene (5 mL). The contents of both syringes were then added to the vigorously stirred boiling solvent at a rate of 1 mmol/h by using a syringe pump. During the reaction, the flask was irradiated with a slide projector lamp (GE ELH, 300 W) at a distance of about 4 cm from the center of the flask. The power source for the lamp was regulated with a variable transformer. Heating and irradiation were continued for 30 min after the addition was complete. The reaction mixture was cooled, and the volatiles were removed by vacuum transfer. The residue was redissolved in ethyl acetate and purified via column chromatography on silica with ethyl acetate with 0–10% methanol as the eluent. The resulting products were recrystallized when obtained as solids or further purified via preparative TLC (Chromatotron) when liquid.

2-Phenyl-5,6,7,8-tetrahydro-3(2*H*)-isoquinolone (6). Phenyl isocyanate (**5**, 0.596 g, 5 mmol) and 1,7-octadiyne[31] (**4**, 0.531 g, 5 mmol) were cocyclized with $CpCo(CO)_2$ (**3**, 95 μL, 0.75 mmol) as described in the general procedure. Purification by column chromatography, followed by sublimation of the resulting solid (130 °C (0.1 mm)) gave **6** as a white powder (0.185 g, 16%): mp 122–125 °C; IR (KBr) 2937, 1672, 1610, 1584, 1280, 853, 766, 703 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.76 (m, 4), 2.54 (br s, 2), 2.70 (br s, 2), 6.41 (s, 1), 7.07 (s, 1), 7.41 (m, 5); mass spectrum, *m/e* 225 (M^+, base, 5.77), 196 (0.93), 169 (3.99), 77 (3.22), 71 (2.72); ^{13}C NMR ($CDCl_3$) δ 22.1, 22.7, 25.2, 28.9, 116.1, 118.6, 126.5, 128.0, 129.0, 134.8, 141.0, 152.4, 161.6.

Anal. Calcd for $C_{15}H_{15}NO$: C, 79.96; H, 6.72; N, 6.22. Found: C, 79.73; H, 6.77; N, 6.08.

2-(β-Phenethyl)-2,5,6,7-tetrahydro-2-pyrindin-3-one (9). This cocyclization was carried out by using 1,6-heptadiyne[31] (**7**, 0.276 g, 3 mmol), β-phenethyl isocyanate[17] (**8**, 0.456 g, 3.1 mmol), and $CpCo(CO)_2$ (57 μL, 0.45 mmol). Purification yielded **9** as a white powder (0.224 g, 31%): mp 117–119 °C; IR (KBr) 2973, 2960, 2943, 1673, 1591, 1341, 707 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.99 (tt, 2, J = 7.3, 7.3), 2.58 (t, 2, J = 7.3), 2.74 (t, 2, J = 7.3), 3.02 (t, 2, J = 7.2), 4.08 (t, 2, $J \approx$ 7.2), 6.45 (s, 1), 6.79 (s, 1), 7.24 (m, 5); mass spectrum, *m/e* 239 (M^+, 4.79), 148 (1.30), 135 (base, 8.00), 120 (0.56), 104 (7.28), 91 (2.89), 77 (4.01).

Anal. Calcd for $C_{16}H_{17}NO$: C, 80.29; H, 7.17; N, 5.85. Found: C, 80.15; H, 7.14; N, 5.86.

3,5-Diethyl-4,6-diphenyl-1-(β-phenethyl)-2(1*H*)-pyridinone (12). When conditions similar to those reported by Hoberg[13b] were used, β-phenethyl isocyanate (736 mg, 5 mmol) in toluene (18 mL) was degassed and added to $Ni(COD)_2$ (0.137 g, 0.5 mmol) and tricyclohexylphosphine (0.140 g, 0.5 mmol) in a 50-mL flask under a nitrogen atmosphere. The solution was cooled to −20 °C and 1-phenyl-1-butyne (1.302 g, 10 mmol) in degassed toluene (3 mL) was added over a period of 1 h. The cooling bath was removed, and the solution was stirred at room temperature for 24 h. After removal of the solvent by vacuum transfer, the residue was washed with ether to leave a white solid. This material was dissolved in CH_2Cl_2 and filtered through a column of silica, eluting with CH_2Cl_2/methanol (5%). The resulting solid was recrystallized to give white crystals of **12** (0.928 g, 46%): mp 193–195 °C; IR (KBr) 2966, 1637, 1603, 1582, 766, 707 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.57 (t, 3, J = 7.4), 1.04 (t, 3, J = 7.4), 1.83 (q,

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2, J = 7.4), 2.35 (q, 2, J = 7.4), 2.90 (m, 2), 3.91 (m, 2), 6.8–7.5 (m, 15); mass spectrum, m/e 407 (M^+, 0.74), 303 (base, 6.12), 302 (5.80), 149 (2.76), 105 (3.68); ^{13}C NMR ($CDCl_3$) δ 13.4, 15.3, 22.2, 22.8, 34.7, 48.6, 119.3, 126.3, 127.3, 128.1 (2 C), 128.2 (2 C), 128.3 (2 C), 128.6 (2 C), 128.7 (2 C), 128.8, 129.4 (2 C), 131.9, 134.7, 138.3, 138.6, 143.1, 150.6, 161.5.

Anal. Calcd for $C_{29}H_{29}NO$: C, 85.45; H, 7.19; N, 3.44. Found: C, 85.83; H, 6.93; N, 3.42.

Cobalt-Catalyzed Cocyclization of β-Phenethyl Isocyanate and 1-Phenyl-1-butyne. This reaction was performed with 5 mmol of isocyanate and 10 mmol of alkyne (with 1 mmol of alkyne in the reaction flask) along with $CpCo(CO)_2$ (200 μL, 1.7 mmol) to give after column chromatography (ether) three compounds, all as white solids. In order of elution: 4,5-diethyl-3,6-diphenyl-1-(β-phenethyl)-2(1*H*)-pyridinone (**13**) (0.952 g, 47%): mp 145–148 °C; IR (KBr) 2978, 1629, 1603, 1573, 1538, 704 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.94 (t, 3, J = 7.4), 1.01 (t, 3, J = 7.4), 2.18 (q, 2, J = 7.4), 2.44 (q, 2, J = 7.4), 2.87 (m, 2), 3.83 (m, 2), 7.1–7.5 (m, 15); mass spectrum, m/e 407 (M^+, 1.96), 316 (0.25), 303 (base, 11.80), 302 (9.88), 288 (2.46), 105 (3.12); ^{13}C NMR ($CDCl_3$) δ 14.7, 15.8, 21.8, 23.4, 34.6, 48.8, 119.4, 126.2, 126.9, 128.2 (2 C), 128.3 (2 C), 128.6 (2 C), 128.7 (2 C), 128.9, 129.2 (2 C). 129.8 (2 C), 130.9, 134.8, 137.3, 138.6, 145.1, 152.2, 161.4.

Anal. Calcd for $C_{29}H_{29}NO$: C, 85.45; H, 7.19; N, 3.44. Found: C, 85.44; H, 7.19; N, 3.43.

Pyridone **12** (0.325 g, 16%): identical with the product obtained from the nickel-catalyzed reaction as described above.

3,6-Diethyl-4,5-diphenyl-1-(β-phenethyl)-2(1*H*)-pyridinone (**14**) (0.272 g, 13%): mp 137–139 °C; IR (KBr) 2988, 1629, 1604, 1575, 1531, 912, 704 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.67 (t, 3, J = 7.4), 1.04 (t, 3, J = 7.4), 2.07 (q, 2, J = 7.4), 2.34 (q, 2, J = 7.4), 3.10 (m, 2), 4.28 (m, 2), 7.2–7.5 (m, 15); mass spectrum, m/e 407 (M^+, 2.13), 303 (11.61), 302 (base, 12.56), 290 (1.00), 288 (0.77), 105 (2.91); ^{13}C NMR ($CDCl_3$) δ 13.9, 14.1, 23.9, 24.5, 35.0, 46.9, 120.7, 126.5, 126.9, 127.4, 128.2, 128.3 (2 C), 128.4 (2 C), 128.5 (2 C), 128.9 (2 C), 130.0 (2 C), 130.8 (2 C), 137.1, 138.1, 138.7, 146.8, 152.0, 162.3.

Anal. Calcd for $C_{29}H_9NO$: C, 85.45; H, 7.19; N, 3.44. Found: C, 85.54; H, 7.20; N, 3.40.

The regiochemical assignments were based on the ^{13}C NMR spectra (^1H coupled and decoupled) compared to the calculated chemical shifts of the carbon resonances[18c] and further compared to known compounds (see text).[18a,b]

5-Hexynoic Acid (28). The procedure used was a modification of that reported by Gilman.[67] To 5-hexyn-1-ol[31] (9.816 g, 100 mmol) in acetone (1000 mL) at 0 °C was added Jones' reagent[68] drop by drop with vigorous stirring until the mixture remained slightly orange. Slow addition was necessary to keep the blue precipitate which was formed from forming a gum, thus stopping the stirrer. The ice bath was removed, and more oxidizing reagent was added to maintain the orange color. After 1 h at room temperature, isopropyl alcohol was added to decompose the excess Jones' reagent. The mixture was filtered through Celite, and the salts were washed several times with acetone. Removal of the solvent by rotary evaporation produced a blue oil (contaminated with chromium salts), which was redissolved in ether, extracted with water, and dried over $MgSO_4$. Evaporation of the ether gave an oil, distillation of which through a Kugelrohr apparatus yielded a colorless oil (9.251 g, 82%): bp 120–125 °C (20 mm) [lit.[26] bp 122–124 °C (20 mm), lit.[69] bp 95–96 °C (6 mm)].

5-Hexynoyl Chloride (29). The original literature[70] procedure (treating the acid with thionyl chloride) was modified with oxalyl chloride.[27] Oxalyl chloride (37.317 g, 294 mmol) and a catalytic amount of DMF was added to a solution of **28** (23.939 g, 196 mmol) in benzene (200 mL) at 25–35 °C for 1–2 h. After removal of the solvent, the residue was purified with a Kugelrohr distillation apparatus to produce **29** as a colorless oil (21.043 g, 82%): bp 50–55 °C (0.5 mm) [lit.[70] bp 39–40 °C, (0.4 mm)]. This procedure resulted in a cleaner product in higher yield (we obtained 69% using thionyl chloride) under milder conditions.

5-Isocyanato-1-pentyne (26a). To 5-hexynoyl chloride (**29**, 21.043 g, 0.161 mol) in dry acetonitrile (200 mL) was added activated sodium azide[28] (11.91 g, 0.177 mol) with stirring under a nitrogen atmosphere. The flask was fitted with a reflux condenser as the reaction mixture began to evolve N_2 immediately. The mixture began to boil to reflux shortly thereafter. After the reaction rate subsided, external heating was applied to keep the solution temperature at 65–75 °C until nitrogen evolution was negligible (30–45 min). The white solid was filtered off, and the yellow solution was distilled at 70 mm (water aspirator with dry ice trap). The isocyanate was collected as a colorless oil (13.003 g, 74%): bp 85 °C (70 mm); IR (neat) 3301, 2284, 2123 cm^{-1}; ^1H NMR (250 MHz, CD_3CN) δ 1.77 (quintet, 2, J = 6.7), 2.21 (t, 1, J = 2.7), 2.28 (dt, 2, J = 2.7, 7.0), 3.44 (t, 2, J = 6.5); mass spectrum, m/e 109 (M^+, 0.21), 108 (2.70), 66 (base, 13.15).

Anal. Calcd for C_6H_7NO: C, 66.03; H, 6.48; N, 12.84. Found: C, 65.80; H, 6.60; N, 13.04.

Methyl 4-Oxo-6-(trimethylsilyl)-5-hexynoate (52). A modification of similar procedures[30] was used to prepare this compound. The anhydrous aluminum chloride (17.835 g, 134 mmol) in dichloromethane (200 mL) at 0 °C was added bis(trimethylsilyl)ethyne (**27a**, 7.978 g, 46.82 mmol) and 3-carbomethoxypropanoyl chloride[96] (**51**, 6.713 g, 44.59 mmol) dissolved in dichloromethane (50 mL) over a period of 30 min. The black solution was allowed to stir at room temperature for 3 h. The mixture was cooled to 0 °C, and 1 M HCl was added cautiously with rapid stirring. Addition was continued until the white precipitate redissolved in the aqueous layer. After warming, the aqueous layer was extracted several times with CH_2Cl_2. The combined organic phase was dried, and the solvent was removed to produce a black oil, which was filtered through a short column of silica, eluting with ether. Distillation of the resulting brown liquid via a Kugelrohr apparatus afforded **52** as a colorless oil (7.831 g, 83%): bp 80–85 °C (0.1 mm); IR (neat) 2961, 2153, 1743, 1683, 1117, 863, 850 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.25 (s, 9), 2.64 (t, 2, J = 6.7), 2.91 (t, 2, J = 6.7), 3.69 (s, 3); mass spectrum, m/e 212 (M^+, 0.05), 197 (5.10), 181 (2.40), 125 (base, 9.02).

Anal. Calcd for $C_{10}H_{16}O_3Si$: C, 56.56; H, 7.61. Found: C, 56.34; H, 7.57.

Methyl 2-[(Trimethylsilyl)ethynyl]-1,3-dioxolane-2-propanoate (53). The ketone **52** (2.123 g, 10 mmol), ethylene glycol (6.207 g, 100 mmol) and *p*-toluenesulfonic acid (0.1 g) were allowed to react in boiling benzene (250 mL) and a water separator was used to remove the azeotrope. The reaction mixture was heated for 5 h, while additional benzene was added occasionally. Analysis by GLC showed the reaction to be complete after this time. Removal of solvent gave an oil which was purified by column chromatography (pentane/ether, 1:1) to produce **53** as a colorless oil (2.48 g, 97%) used directly in the next step: IR (neat) 2960, 2899, 2169, 1743, 1440, 1254, 1100, 866, 848 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ 0.21 (s, 9), 2.24 (m, 4), 3.54 (s, 3), 3.87 (m, 4).

2-Ethynyl-1,3-dioxolane-2-propanoic Acid (54). The procedure of Warren and Weedon[37] was utilized to hydrolyze the ester portion of **53** (23.716 g, 92 mmol) in the presence of the ketal. The trimethylsilyl group was cleaved simultaneously. Recrystallization from ether/hexane gave white crystals (12.962 g, 83%): mp 93–95.5 °C; IR (KBr) 3261, 3000, 2103, 1710 cm^{-1}; ^1H NMR (90 MHz, acetone-d_6) δ 2.20 (m, 2), 2.50 (m, 2), 3.07 (s, 1), 4.03 (br s, 4), 8.01 (br s, 1); mass spectrum, m/e 169 (M − 1, 0.07), 153 (0.63), 125 (2.94), 109 (2.78), 97 (4.58), 53 (base, 6.04).

Anal. Calcd for $C_8H_{10}O_4$: C, 56.46; H, 5.93. Found: C, 56.40; H, 5.93.

2-Ethynyl-1,3-dioxolane-2-propionyl Chloride (55). The acid **54** (1.702 g, 10 mmol) was treated with oxalyl chloride (1.907 g, 15 mmol) and DMF as described previously for **29**. Distillation via a Kugelrohr apparatus yielded **55** as a colorless oil (1.547 g, 82%): bp 90–95 °C (0.2 mm); IR (neat) 3292, 2901, 2113, 1805, 1200, 1030, 949 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.32 (t, 2, J = 7.3), 2.50 (s, 1), 3.06 (t, 2, J = 7.3), 4.02 (m, 4); mass spectrum, m/e 189 (M + 1, 0.11), 163 (0.22), 153 (3.95), 125 (2.52), 109 (3.28), 97 (5.63), 53 (base, 7.55); exact mass calcd for $C_8H_9O_3$ (M − Cl) 153.0552, found 153.0551.

2-(2-Ethynyl-1,3-dioxolan-2-yl)ethyl Isocyanate (26b). The acid chloride **55** (2.830 g, 15 mmol) was allowed to react with

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sodium azide (1.073 g, 16.5 mmol) in acetonitrile in the manner described for **26a**. Distillation through a Kugelrohr apparatus furnished a colorless oil (2.114g, 84%): bp 80–85 °C (0.2 mm); IR (neat) 3289, 2974, 2901, 2278, 2113, 1199, 1034, 950, 671 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.25 (t, 2, J = 6.9), 2.75 (s, 1), 3.52 (t, 2, J = 6.9), 4.07 (m, 4); mass spectrum, m/e 167 (M^+, 0.21), 142 (0.86), 133 (3.19), 124 (1.45), 97 (5.77), 56 (5.41), 53 (base, 6.50); ^{13}C NMR ($CDCl_3$) δ 38.07, 40.23, 64.85, 72.82, 77.49, 80.83, 101.23.

Anal. Calcd for $C_8H_9NO_3$: C, 57.47; H, 5.44; N, 8.38. Found: C, 57.09; H, 5.40; N, 8.19.

2,3-Dihydro-6,7-bis(trimethylsilyl)-5(1*H*)-indolizinone (30). Isocyanate **26a** (0.573 g, 5.26 mmol) was cocyclized with bis(trimethylsilyl)ethyne (BTMSA, **27a**, used as the solvent) in the presence of cobalt catalyst (100 μL, 0.79 mmol) to give **30** as a white solid (1.063 g, 72%): mp 117–119 °C; IR (KBr) 2951, 1623, 1573, 1250, 840 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.33 (s, 9), 0.36 (s, 9), 2.13 (tt, 2, J = 7.8, 7.5), 3.05 (t, 2, J = 7.8), 4.09 (t, 2, J = 7.5), 6.32 (s, 1); mass spectrum, m/e 279 (M^+, 4.80), 264 (base, 23.55), 236 (1.99), 73 (7.28).

Anal. Calcd for $C_{14}H_{25}NOSi_2$: C, 60.14; H, 9.03; N, 5.01. Found: C, 59.94; H, 8.84; N, 4.95.

A small amount of this pyridone was treated with trifluoroacetic acid (excess) in ether for 2 h at room temperature. Neutralization with sodium carbonate and water, followed by extraction with ether, gave monosilylated indolizinone **42**: ^1H NMR (250 MHz, $CDCl_3$) δ (from $CHCl_3$, 7.24) 0.21 (s, 9), 2.13 (tt, 2, J = 7.2, 7.7), 3.04 (t, 2, J = 7.7), 4.09 (t, 2, J = 7.2), 6.14 (s, 1), 6.52 (s, 1).

2,3-Dihydro-7-propyl-6-(trimethylsilyl)-5(1*H*)-indolizinone (31) and 2,3-Dihydro-6-propyl-7-(trimethylsilyl)-5(1*H*)-indolizinone (32). Isocyanate **26a** (0.546 g, 5 mmol) was exposed to alkyne **27b** (2.102 g, 15 mmol) and catalyst **3** (114 μL, 0.9 mmol) to furnish **31** as an off-white solid (0.842 g, 68%): mp 64–66 °C; IR (KBr) 2960, 1637, 1579, 1517, 1241, 843 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ (from $CHCl_3$, δ 7.24 ppm) 0.29 (s, 9), 0.92 (t, 3, J = 7.3), 1.48 (m, 2), 2.08 (tt, 2, J = 7.2, 7.7), 2.44 (m, 2), 2.97 (t, 2, J = 7.7), 4.02 (t, 2, J = 7.2), 5.92 (s, 1); mass spectrum, m/e 249 (M^+, 0.99), 234 (6.77), 77 (base, 25.72), 47 (6.22).

Anal. Calcd for $C_{14}H_{23}NOSi$: C, 67.40; H, 9.31; N, 5.62. Found: C, 67.23; H, 9.21; N, 5.59.

The lower R_f fraction was the other regioisomer **32**, a waxy solid (0.056 g, 5%): mp 115–125 °C; IR (KBr) 2964, 1632, 1586, 1248, 856, 845 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ (from $CHCl_3$, 7.24) 0.26 (s, 9), 0.97 (t, 3, J = 7.3), 1.54 (m, 2), 2.12 (tt, 2, J = 7.2, 7.7), 2.54 (m, 2), 3.01 (t, 2, J = 7.7), 4.10 (t, 2, J = 7.2), 6.10 (s, 1); mass spectrum, m/e 249 (M^+, 3.54), 234 (6.22), 220 (base, 7.61), 219 (0.71), 206 (1.23), 176 (2.86), 149 (1.65), 73 (3.18).

Anal. Calcd for $C_{14}H_{23}NOSi$: C, 67.40; H, 9.31; N, 5.62. Found: C, 67.17; H, 9.16; N, 5.47.

2,3-Dihydro-7-propyl-5(1*H*)-indolizinone (38). Indolizinone **31** (0.374 g, 1.5 mmol) was treated with trifluoroacetic acid (0.855 g, 7.5 mmol) in boiling benzene for 1 h. Workup with sodium carbonate, followed by chromatography produced **38** as an oil (0.104 g, 39%): IR (neat) 1659, 1574 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.94 (t, 3, J = 7.3), 1.63 (m, 2), 2.21 (tt, 2, J = 7.3, 7.7), 2.44 (m, 2), 3.09 (t, 2, J = 7.7), 4.16 (t, 2, J = 7.3), 6.13 (d, 1, J = 1.0), 6.36 (d, 1, J = 1.0); mass spectrum, m/e 177 (M^+, 9.27), 162 (3.14), 148 (base, 17.83), 120 (8.02); exact mass calcd for $C_{11}H_{15}NO$ 177.1154, found 177.1148.

2,3-Dihydro-6-propyl-5(1*H*)-indolizinone (39). Indolizinone **32** (0.006 g, 0.024 mmol) was treated with tetramethylammonium fluoride trihydrate (0.071 g, 0.48 mmol) in Me_2SO (3 mL) at 60–65 °C for 2 h.[71] Aqueous workup produced **39** as an oil (0.004 g, 90%): IR ($CHCl_3$) 3014, 1650, 1581, 1569, 1232 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.95 (t, 3, J = 7.3), 1.60 (m, 2), 2.17 (tt, 2, J = 7.2, 7.6), 2.49 (t, 2, J = 7.5), 3.05 (t, 2, J = 7.6), 4.15 (t, 2, J = 7.2), 6.05 (d, 1, J = 6.8), 7.14 (d, 1, J = 6.8); mass spectrum, m/e 177 (M^+, 6.24), 162 (8.47), 149 (9.83), 148 (base, 12.43); exact mass calcd for $C_{11}H_{15}NO$ 177.1154, found 177.1151.

2-[5-Oxo-1,2,3,5-tetrahydro-6-(trimethylsilyl)indolizin-7-yl]-2-ethyl-1,3-dioxolane (33). Alkyne **27c** was prepared by ketalization of the known ketone[30] under standard conditions. This alkyne (1.949 g, 9.8 mmol) was cyclized with **26a** (0.327 g, 3 mmol) with $CpCo(CO)_2$ (114 μL, 0.9 mmol) to result in **33** as a white solid (0.698 g, 76%): mp 150–152 °C; IR (KBr) 1629, 1589 1150 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.29 (s, 9), 0.94 (t, 3, J = 7.3), 1.87 (q, 2, J = 7.3), 2.11 (tt, 2, J = 7.3, 7.4), 3.00 (t, 2, J = 7.4), 3.63 (m, 2), 3.89 (m, 2), 4.03 (t, 2, J = 7.3), 6.32 (s, 1); mass spectrum, m/e 307 (M^+, 1.16), 292 (7.83), 276 (8.90), 248 (base, 25.83), 232 (9.69).

Anal. Calcd for $C_{16}H_{25}NO_3Si$: C, 62.49; H, 8.21; N, 4.56. Found: C, 62.30; H, 7.99; N, 4.50.

2,3-Dihydro-7-*tert*-butyl-5(1*H*)-indolizinone (34). Alkyne **27d** was prepared from *tert*-butylacetylene[72] by silylation of the anion with trimethylsilyl chloride:[29] bp 124–125 °C; ^1H NMR (250 MHz, $CDCl_3$) δ (from $CHCl_3$, 7.24) 0.11 (s, 9), 1.19 (s, 9). This alkyne (1.316 g, 15 mmol) was cocyclized with **26a** with $CpCo(CO)_2$ (114 μL, 0.9 mmol) as the catalyst to give after sublimation a white solid (0.165 g, 17%): mp 79–81 °C; IR (KBr) 1660, 1651, 1647, 1579, 1524, 858 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.23 (s, 9), 2.18 (tt, 2, J = 7.3, 7.7), 3.06 (t, 2, J = 7.7), 4.10 (t, 2, J = 7.3), 6.18 (s, 1), 6.36 (s, 1); mass spectrum, m/e 191 (M^+, 7.58), 176 (base, 8.12), 149 (5.18).

Anal. Calcd for $C_{12}H_{17}NO$: C, 75.34; H, 8.98; N, 7.32. Found: C, 75.04; H, 8.87; N, 7.29.

The ^1H NMR spectrum of a latter chromatography fraction (~5 mg, <1%) exhibited signals at δ 6.09 (d, 1, J = 6.8) and 7.20 (d, 1, J = 6.8) ppm, characteristic of desilylated **35**.

2-(6-Ethyl-5-oxo-1,2,3,5-tetrahydroindolizin-7-yl)-2-methyl-1,3-dioxolane (36) and 2-(7-Ethyl-5-oxo-1,2,3,5-tetrahydroindolizin-6-yl)-2-methyl-1,3-dioxolane (37). Ketal **27e** was prepared by treatment of the commercially available[31] ethynyl ketone with ethylene glycol under the usual conditions. This alkyne (1.849 g, 11.5 mmol) was cocyclized with **26a** (0.546 g, 5 mmol) in the presence of $CpCo(CO)_2$ (114 μL, 0.9 mmol). Separation by chromatography on alumina (activity III, ethyl acetate) gave a mixture of isomers. The higher R_f compound (an oil) was tentatively identified as **36** (0.516 g, 41%): IR (neat) 1647, 1600, 1587 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.15 (t, 3, J = 7.2), 1.62 (s, 3), 2.17 (tt, 2, J = 7.3, 7.7), 2.76 (q, 2, J = 7.2), 3.04 (t, 2, J = 7.7), 3.78 (m, 2), 4.03 (m, 2), 4.15 (t, 2, J = 7.3), 6.36 (s, 1); mass spectrum, m/e 249 (M^+, 3.29), 234 (1.58), 206 (3.20), 204 (3.57), 177 (2.49), 87 (base, 7.67); ^{13}C NMR ($CDCl_3$) δ 13.4, 21.2, 21.6, 26.4, 31.7, 48.8, 64.4, 77.4, 99.1, 108.6, 129.0, 146.2, 150.3, 162.6; exact mass calcd for $C_{14}H_{19}NO_3$ 249.1365, found 249.1362.

The lower R_f compound, also an oil, was assigned the structure of the regioisomer **37** (0.426 g, 31%): IR (neat) 1650, 1598, 1580 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.74 (t, 3, J = 7.4), 1.79 (s, 3), 2.13 (tt, 2, J = 7.2, 7.7), 2.79 (q, 2, J = 7.4), 3.01 (t, 2, J = 7.7), 3.82 (m, 2), 4.01 (m, 2), 4.10 (t, 2, J = 7.2), 5.90 (s, 1); mass spectrum, m/e 249 (M^+, 1.24), 234 (base, 11.65), 206 (4.24), 204 (4.26), 190 (4.23), 87 (5.35); ^{13}C NMR ($CDCl_3$) δ 15.5, 22.0, 25.0, 27.5, 32.0, 49.0, 64.5, 77.5, 104.0, 110.5, 126.0, 148.0, 153.5, 160.5; exact mass calcd for $C_{14}H_{19}NO_3$ 249.1365, found 249.1362.

The regioisomeric assignments were confirmed by ^{13}C NMR analysis of the hydrolyzed products **40** and **41** (see text and below).

7-Acetyl-2,3-dihydro-6-ethyl-5(1*H*)-indolizinone (40). Indolizinone **36** (0.516 g, 2.07 mmol) was dissolved in ethanol/water (1:1), oxalic acid dihydrate (approximately 0.1 g) was added, and the mixture was heated at reflux for 1 h. After aqueous bicarbonate workup, recrystallization of the resulting solid afforded light yellow crystals of **40** (0.319 g, 75%): mp 86–88 °C; IR ($CHCl_3$) 3000, 1705, 1651, 1595, 1584 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.15 (t, 3, J = 7.4), 2.20 (tt, 2, J = 7.3, 7.7), 2.47 (s, 3), 2.57 (q, 2, J = 7.4), 3.08 (t, 2, J = 7.7), 4.15 (t, 2, J = 7.3), 6.02 (s, 1); mass spectrum, m/e 205 (M^+, 2.65), 190 (4.78), 162 (2.18), 57 (base, 8.89); ^{13}C NMR ($CDCl_3$) δ 13.2, 20.1, 20.8, 29.8, 31.1, 48.4, 97.1, 127.4, 147.2, 147.4, 161.2, 202.4.

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.21; H, 7.38; N, 6.82. Found: C, 70.08; H, 7.43; N, 6.70.

6-Acetyl-2,3-dihydro-7-ethyl-5(1*H*)-indolizinone (41). The hydrolysis of the ketal **37** (0.227 g, 0.9 mmol) was performed as described above to give **41** as an oil (0.187 g, 99%): IR ($CHCl_3$) 3003, 1684, 1646, 1593, 1575 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.17 (t, 3, J = 7.5), 2.21 (quintet, 2, J = 7.6), 2.52 (q, 2, J = 7.5), 2.57 (s, 3), 3.09 (t, 2, J = 8.0), 4.13 (t, 2, J = 7.3), 6.07 (s, 1); mass

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spectrum, *m/e* 205 (M^+, 5.03), 190 (base, 13.27), 186 (3.08), 177 (0.19), 162 (2.03); ^{13}C NMR ($CDCl_3$) δ 14.2, 20.4, 26.1, 30.8, 31.3, 48.1, 102.6, 125.7, 151.2, 156.5, 159.5, 202.1; exact mass calcd for $C_{12}H_{15}NO_2$ 205.1103, found 205.1102.

2′,3′-Dihydro-6′,7′-bis(trimethylsilyl)-5′-oxospiro[1,3-dioxolane-2,1′(5′*H*)-indolizine] (56). Isocyanate **26b** (0.836 g, 5 mmol) was cocyclized with BTMSA (**27a**, used as the solvent) in the presence of $CpCo(CO)_2$ (159 μL, 1.25 mmol). The residue was purified to give a white solid (1.154 g, 68%): mp 133.5–134.5 °C; IR (KBr) 2953, 2896, 1632, 1586, 1407 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ (from $CHCl_3$, 7.24) 0.31 (s, 9), 0.33 (s, 9), 2.30 (t, 2, *J* = 6.9), 4.03 (t, 2, *J* = 6.9), 4.11 (m, 4), 6.39 (s, 1); mass spectrum, *m/e* 337 (M^+, 2.74), 322 (base, 11.03), 294 (1.56), 73 (8.07).

Anal. Calcd for $C_{16}H_{27}NO_3Si_2 \cdot H_2O$: C, 55.44; H, 8.16; N, 4.04. Found: C, 55.69; H, 7.96; N, 3.97.

2′,3′-Dihydro-5′-oxo-7′-propyl-6′-(trimethylsilyl)spiro[1,3-dioxolane-2,1′(5′*H*)-indolizine] (57) and 2′,3′-Dihydro-5′-oxo-6′-propyl-7′-(trimethylsilyl)spiro[1,3-dioxolane-2,1′(5′*H*)-indolizine] (58). Alkyne **27b** (used as the solvent) was cyclized in the presence of 114 μL (0.9 mmol) of cobalt catalyst with isocyanate **26b** (0.502 g, 3 mmol) to produce a mixture of regioisomers. Separation by column chromatography and recrystallization of the higher R_f fraction afforded **57** as a solid (0.555 g, 60%): mp 87–89.5 °C; IR (KBr) 2904, 1643, 1592, 1034, 858, 846, 644 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ (from $CHCl_3$, 7.24) 0.31 (s, 9), 0.95 (t, 3, *J* = 7.3), 1.52 (m, 2), 2.31 (t, 2, *J* = 6.8), 2.50 (m, 2), 4.01 (t, 2, *J* = 6.8), 4.10 (m, 4), 6.04 (s, 1); mass spectrum, *m/e* 307 (M^+, 3.99), 292 (base, 11.03), 276 (6.13), 264 (1.59), 248 (0.89), 192 (2.72), 73 (2.82).

Anal. Calcd for $C_{16}H_{25}NO_3Si$: C, 62.52; H, 8.22; N, 4.56. Found: C, 62.44; H, 7.89; N, 4.43.

The lower R_f fraction, an oil, was identified as **58** (0.028 g, 3%): IR ($CHCl_3$) 2967, 1643, 1586, 1313, 1255, 846 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ (from $CHCl_3$, 7.24) 0.26 (s, 9), 0.96 (t, 3, *J* = 7.3), 1.52 (m, 2), 2.30 (t, 2, *J* = 7.0), 2.56 (m, 2), 4.10 (m, 6), 6.24 (s, 1); mass spectrum, *m/e* 307 (M^+, 3.40), 292 (4.28), 279 (4.41), 278 (base, 4.70), 264 (0.98), 234 (2.88); exact mass calcd for $C_{16}H_{25}NO_3Si$ 307.1603, found 307.1600.

2′,3′-Dihydro-5′-oxo-7′-propylspiro[1,3-dioxolane-2,1′(5′*H*)-indolizine] (63). Treatment of a small amount of **57** (~10 mg) with trifluoroacetic acid in boiling benzene in the same manner as for **38** gave **63** as an oil: IR ($CHCl_3$) 2997, 1669, 1591, 1317, 1183, 1038 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.94 (t, 3, *J* = 3.7), 1.62 (m, 2), 2.37 (t, 2, *J* = 7.0), 2.45 (t, 2, *J* = 7.6), 4.09 (t, 2, *J* = 7.0), 4.13 (m, 4), 6.11 (d, 1, *J* = 1.1), 6.35 (d, 1, *J* = 1.1); mass spectrum, *m/e* 235 (M^+, 5.08), 207 (3.59), 163 (3.49), 99 (base, 5.33), 55 (4.42); exact mass calcd for $C_{13}H_{17}NO_3$ 235.1208, found 235.1209.

2,3-Dihydro-7-propyl-6-(trimethylsilyl)-1,5-indolizinedione (64). To an ether solution of **57** (~10 mg) was added 6 N HCl (excess), and the solution was stirred overnight at room temperature. Neutralization and extraction with ether, followed by chromatography, afforded **64** as an oil: IR (neat) 2962, 1742, 1642, 1602, 848 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ (from $CHCl_3$, 7.24) 0.35 (s, 9), 0.96 (t, 3, *J* = 7.3), 1.53 (quintet, 2, *J* = 7.9), 2.59 (t, 2, *J* = 7.9), 2.83 (t, 2, *J* = 7.0), 4.20 (t, 2, *J* = 7.0), 6.67 (s, 1); mass spectrum, *m/e* 263 (M^+, 3.91), 248 (base, 28.85), 232 (12.34), 192 (11.36); exact mass calcd for $C_{14}H_{21}NO_2Si$ 263.1342, found 263.1348.

2′,3′-Dihydro-6′-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-5′-oxo-7′-propylspiro[1,3-dioxolane-2,1′(5′*H*)-indolizine] (59) and 2′,3′-Dihydro-7′-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-5′-oxo-6′-propylspiro[1,3-dioxolane-2,1′(5′*H*)-indolizine] (60). Alkyne **27f** was prepared in 39% yield by treating 2-hexyn-1-ol[31] with *tert*-butyldiphenylsilyl chloride and imidazole in DMF:[38] ^1H NMR (250 MHz, $CDCl_3$) δ 0.95 (t, 3, *J* = 7.3), 1.06 (s, 9), 1.48 (qt, 2, *J* = 7.0, 7.3), 2.14 (tt, 2, *J* = 2.1, 7.0), 4.31 (t, 2, *J* = 2.1), 7.40 (m, 6), 7.72 (m, 4). Cyclization of this alkyne (3.029 g, 9 mmol) with **26b** (0.502 g, 3 mmol) and $CpCo(CO)_2$ (114 μL, 0.9 mmol) gave **59** as a white solid (0.302 g, 20%): mp 165–167 °C; IR ($CHCl_3$) 2966, 1659, 1594, 1115, 1054, 704 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.91 (t, 3, *J* = 7.3), 1.05 (s, 9), 1.56 (m, 2), 2.34 (t, 2, *J* = 6.8), 2.55 (m, 2), 4.05 (t, 2, *J* = 6.8), 4.13 (m, 4), 4.73 (s, 2), 6.10 (s, 1), 7.39 (m, 6), 7.76 (m, 4); mass spectrum, *m/e* 503 (M^+, 0.06), 446 (base, 7.22), 418 (0.30), 199 (6.66), 99 (2.06), 77 (1.61), 57 (3.66).

Anal. Calcd for $C_{30}H_{37}NO_4Si$: C, 71.52; H, 7.42; N, 2.78. Found: C, 71.22; H, 7.48; N, 2.75.

The other regioisomer, **60**, was obtained as a gummy oil (0.267 g, 18%): IR ($CHCl_3$) 2965, 1657, 1591, 1114, 1108, 1092 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.80 (t, 3, *J* = 7.3), 1.10 (s, 9), 1.33 (m, 2), 2.30 (m, 2), 2.40 (t, 2, *J* = 6.9), 4.13 (m, 6), 4.67 (s, 2), 6.73 (s, 1), 7.42 (m, 6), 7.67 (m, 4); mass spectrum, *m/e* 503 (M^+, 0.53), 446 (1.10), 199 (base, 6.66), 99 (2.73), 77 (4.50), 57 (2.50); exact mass calcd for $C_{30}H_{37}NO_4Si$ 503.2492, found 503.2511.

The regioisomeric assignment of **59** was confirmed by converting it into alcohol **82** by desilylation with tetrabutylammonium fluoride in THF, which was further oxidized to aldehyde **81** (see below).

2′,3′-Dihydro-7′-methyl-5′-oxospiro[1,3-dioxolane-2,1′-(5′*H*)-indolizine]-6′-carboxylic Acid, Ethyl Ester (61) and 2′,3′-Dihydro-6′-methyl-5′-oxospiro[1,3-dioxolane-2,1′-(5′*H*)-indolizine]-7′-carboxylic Acid, Ethyl Ester (62). These compounds were obtained from the cyclization of alkyne **27g**[15a] (1.254 g, 11 mmol) with isocyanate **26b** (0.748 g, 4.5 mmol). Purification by chromatography (Waters Prep LC 500, ethyl acetate) and recrystallization afforded (in order of elution) **62** as a white solid (0.213 g, 17%): mp 95.5–97 °C; IR (KBr) 1723, 1657, 1605, 1253, 1232, 1201, 1063 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.39 (t, 3, *J* = 7.0), 2.37 (s, 3), 2.39 (t, 2, *J* = 7.0), 4.13 (t, 2, *J* = 7.0), 4.14 (m, 4), 4.37 (q, 2, *J* = 7.0), 6.51 (s, 1); mass spectrum, *m/e* 279 (M^+, 6.73), 250 (base, 7.00), 234 (2.29), 207 (5.37), 99 (6.29), 55 (4.28). The other regioisomer (**61**, 0.180 g, 14%) was identical with the compound prepared by Shamma.[27]

Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.20; H, 6.15; N, 5.02. Found: C, 60.12; H, 6.21; N, 4.98.

2,3-Dihydro-8-[(*N*,*N*-dimethylamino)methyl]-7-propyl-6-(trimethylsilyl)-5(1*H*)-indolizinone (65). To the pyridone **31** (0.035 g, 0.14 mmol) and dimethylmethyleneiminium chloride[46] (0.025 g, 0.27 mmol) in a flask under nitrogen was added DMF (1 mL) and the mixture was heated 1 h at 80 °C. Aqueous workup and chromatography on alumina (activity II, 25% ethyl acetate/dichloromethane) gave **65** as a colorless oil (0.014 g, 33%): IR (neat) 2964, 1635, 1588, 1261, 1243, 1023, 845, 797 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ (from $CHCl_3$, 7.24) 0.31 (s, 9), 0.97 (t, 3, *J* = 7.3), 1.40 (m, 2), 2.09 (tt, 2, *J* = 7.3, 7.7), 2.18 (s, 6), 2.66 (m, 2), 3.06 (t, 2, *J* = 7.7), 3.08 (s, 2), 4.06 (t, 2, *J* = 7.3); mass spectrum, *m/e* 306 (M^+, 0.52), 291 (0.61), 262 (base, 8.72), 261 (6.15), 246 (6.97); exact mass calcd for $C_{17}H_{30}N_2OSi$ 306.2127, found 306.2134.

6-Bromo-2,3-dihydro-7-propyl-5(1*H*)-indolizinone (66). To a solution of pyridone **31** (0.336 g, 1.35 mmol) in dichloromethane at 0 °C was added bromine in CCl_4 (2.7 mL, 1.35 mmol) dropwise with stirring. The mixture was warmed to room temperature, and a few more drops of bromine solution were added to drive the reaction to completion (monitored by TLC). Extraction with sodium bisulfite was followed by aqueous and NaCl (saturated) workup to give a solid which was recrystallized from hexane to yield tan crystals of **66** (0.252 g, 73%): mp 108–109 °C; IR (KBr) 1643, 1590, 1424, 1122 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.99 (t, 3, *J* = 7.3), 1.62 (m, 2), 2.20 (tt, 2, *J* = 7.3, 7.7), 2.62 (t, 2, *J* = 7.7), 3.04 (t, 2, *J* = 7.7), 4.17 (t, 2, *J* = 7.3), 6.04 (s, 1); mass spectrum, *m/e* 257 (M + 1, 5.60), 255 (M − 1, 5.75), 229 (3.63), 227 (3.77), 200 (1.33), 198 (1.47), 148 (3.56), 120 (base, 6.51).

Anal. Calcd for $C_{11}H_{14}NOBr$: C, 51.57; H, 5.52; N, 5.47. Found: C, 51.60; H, 5.61; N, 5.48.

6,8-Dibromo-2,3-dihydro-7-propyl-5(1*H*)-indolizinone (67). An excess of Br_2 in CCl_4 was added to indolizinone **31** (0.048 g, 0.19 mmol) in dichloromethane at room temperature. The reaction mixture was worked up as described for **66** and purified by preparative TLC (ethyl acetate/methanol, 20:1) to give an oil which was crystallized to produce white crystals of **67** (0.060 g, 94%): mp 92–94 °C; IR ($CHCl_3$) 3003, 2970, 1647, 1590, 1133 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.05 (t, 3, *J* = 7.3), 1.58 (m, 2), 2.24 (tt, 2, *J* = 7.5, 7.9), 2.86 (m, 2), 3.15 (t, 2, *J* = 7.9), 4.29 (t, 2, *J* = 7.5); mass spectrum, *m/e* 335 (M^+, base, 4.09), 333 (2.15), 309 (0.96), 307 (1.94), 305 (1.12).

Anal. Calcd for $C_{11}H_{13}NOBr_2$: C, 39.42; H, 3.92; N, 4.18. Found: C, 39.78; H, 4.07; N, 4.12.

Bromination of 38. Bromine in CCl_4 (0.5 M, 1.18 mL, 0.59 mmol) was added dropwise to a solution of indolizinone **38** (0.104 g, 0.59 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After warming to room

temperature, the reaction mixture was worked up as described for **66**. Partial separation of the product mixture was achieved by preparative TLC (silica, 10% methanol/CH_2Cl_2) and the fractions were analyzed by ^1H NMR spectroscopy. Integration of the signals characteristic of each indolizinone component established the following percentages of compounds in the reaction mixture: **68**, 36% [^1H NMR (250 MHz, $CDCl_3$) δ 0.99 (t, 3, J = 7.3), 1.60 (m, 2), 2.23 (tt, 2, J = 7.4, 7.9), 2.52 (t, 2, J = 7.4), 3.15 (t, 2, J = 7.9), 4.23 (t, 2, J = 7.4), 6.30 (s, 1)]; **66**, 7%; **67**, 15%; **38**, 40%.

2-(6-Bromo-5-oxo-1,2,3,5-tetrahydroindolizin-7-yl)-2-ethyl-1,3-dioxolane (69). To the indolizinone **33** (0.167 g, 0.54 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added pyridine (88 μL, 1.09 mmol) and Br_2/CCl_4 (0.5 M, 1.3 mL, 0.65 mmol) dropwise with stirring. The solution was allowed to warm to room temperature, and was worked up in the same manner as **66**. Purification afforded **69** as pale yellow crystals (0.119 g, 70%): mp 113–115 °C; IR (KBr) 1659, 1652, 1600 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.91 (t, 3, J = 7.4), 2.12 (q, 2, J = 7.4), 2.22 (tt, 2, J = 7.3, 7.7), 3.07 (t, 2, J = 7.7), 3.78 (m, 2), 4.04 (m, 2), 4.18 (t, 2, J = 7.3), 6.44 (s, 1); mass spectrum, m/e 315 (M + 1, 0.44), 313 (M − 1, 0.52), 286 (2.39), 284 (2.61), 101 (6.77), 57 (base, 9.40).

Anal. Calcd for $C_{13}H_{16}NO_3Br$: C, 49.69; H, 5.15; N, 4.46. Found: C, 49.75; H, 5.20; N, 4.38.

2,3-Dihydro-6-iodo-7-(trimethylsilyl)-5(1*H*)-indolizinone (70). A solution of ICl in CCl_4 (0.69 M, 0.63 mL, 0.44 mmol) was added dropwise to a solution of indolizinone **30** (0.122 g, 0.44 mmol) in dichloromethane at 0 °C with stirring. The color faded immediately to pale yellow with each drop. The reaction mixture was warmed to room temperature and monitored by TLC until no starting material remained. The solution was washed with sodium thiosulfate, water, and saturated NaCl and dried over $MgSO_4$. Removal of solvent by rotary evaporation gave a solid which was crystallized from dichloromethane/hexane to afford pale yellow crystals of **70** (0.138 g, 94%): mp 167–168.5 °C; IR (KBr) 1635, 1585, 1246, 846 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.41 (s, 9), 2.17 (tt, 2, J = 7.3, 7.7), 3.05 (t, 2, J = 7.7), 4.18 (t, 2, J = 7.3), 6.12 (s, 1); mass spectrum, m/e 333 (M$^+$, base, 32.94), 318 (22.34), 290 (1.58), 206 (1.41), 190 (5.86), 176 (1.49), 159 (2.52).

Anal. Calcd for $C_{11}H_{16}NOSiI$: C, 39.64; H, 4.85; N, 4.20. Found: C, 39.86; H, 4.86; N, 4.07.

2,3-Dihydro-6-iodo-7-propyl-5(1*H*)-indolizinone (71). Indolizinone **31** (0.177 g, 0.71 mmol) was allowed to react with ICl (0.69 M in CCl_4, 1.2 mL, 0.83 mmol) in the same manner as described for **70**. Workup and recrystallization gave **71** as tan crystals (0.142 g, 66%): mp 85.5–87 °C; IR (KBr) 2958, 1635, 1584 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.00 (t, 3, J = 7.3), 1.60 (m, 2), 2.19 (tt, 2, J = 7.2, 7.6), 2.64 (m, 2), 3.03 (t, 2, J = 7.6), 4.16 (t, 2, J = 7.2), 6.05 (s, 1); mass spectrum, m/e 303 (M$^+$, base, 35.53), 288 (0.60), 275 (4.91), 246 (8.38), 176 (5.41), 148 (8.17), 120 (6.80).

Anal. Calcd for $C_{11}H_{14}NOI$: C, 43.58; H, 4.66; N, 4.62. Found: C, 43.75; H, 4.65; N, 4.40.

2-(6-Iodo-5-oxo-1,2,3,5-tetrahydroindolizin-7-yl)-2-ethyl-1,3-dioxolane (72). The pyridone **33** (0.180 g, 0.59 mmol) was treated with ICl (0.69 M in CCl_4, 1 mL, 0.69 mmol) as described for **69** to give pale yellow crystals of **72** (0.200 g, 94%): mp 101–104 °C; IR (KBr) 1642, 1595, 1200, 1042, 936 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.93 (t, 3, J = 7.4), 2.11 (q, 2, J = 7.4), 2.22 (tt, 2, J = 7.3, 7.7), 3.08 (t, 2, J = 7.7), 3.74 (m, 2), 4.02 (m, 2), 4.18 (t, 2, J = 7.3), 6.45 (s, 1); mass spectrum, m/e 361 (M$^+$, 2.4), 333 (0.6), 332 (5.2), 288 (1.0), 260 (1.1), 206 (3.0), 162 (1.5), 134 (3.1), 101 (base, 20.1).

Anal. Calcd for $C_{13}H_{16}NO_3I$: C, 43.23; H, 4.47; N, 3.88. Found: C, 43.42; H, 4.54; N, 3.80.

2′,3′-Dihydro-6′-iodo-7′-(trimethylsilyl)-5′-oxospiro[1,3-dioxolane-2,1′(5′*H*)-indolizine] (73). A solution in ICl in CCl_4 was added to indolizinone **56** (0.815 g, 2.41 mmol) dissolved in dichloromethane at 0 °C until the solution maintained a slightly red color. After workup, crystallization gave yellow crystals of **73** (0.813 g, 86%): mp 144–145 °C; IR (KBr) 2954, 2906, 1643, 1635, 1597, 1319, 1254, 1195, 1072, 1034, 950, 892, 838 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.43 (s, 9), 2.35 (t, 2, J = 7.0), 4.15 (m, 6), 6.21 (s, 1); mass spectrum, m/e 391 (M$^+$, base, 23.76), 376 (6.94), 348 (2.12), 99 (4.68).

Anal. Calcd for $C_{13}H_{18}NO_3SiI$: C, 39.90; H, 4.65; N, 3.58. Found: C, 39.84; H, 4.69; N, 3.51.

2′,3′-Dihydro-6′-iodo-7′-propyl-5′-oxospiro[1,3-dioxolane-2,1′(5′*H*)-indolizine] (74). The reaction was performed in the same manner as that involving **72** by using indolizinone **57** (0.686 g, 2.03 mmol) and ICl (0.45 M in CCl_4, 5 mL, 2.20 mmol) to afford pale yellow crystals of **74** (0.682 g, 93%): mp 114–116 °C; IR (KBr) 2962, 1646, 1597, 1318, 1102, 1076, 1032, 927 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.02 (t, 3, J = 7.3), 1.62 (m, 2), 2.37 (t, 2, J = 7.0), 2.69 (m, 2), 4.13 (m, 6), 6.15 (s, 1); mass spectrum, m/e 361 (M$^+$, base, 36.08), 333 (1.57), 289 (9.34), 207 (4.24), 178 (3.25).

Anal. Calcd for $C_{13}H_{16}NO_3I$: C, 43.19; H, 4.47; N, 3.88. Found: C, 43.31; H, 4.45; N, 3.78.

2,3-Dihydro-6-(phenylethynyl)-7-propyl-5(1*H*)-indolizinone (75). Triethylamine (15 mL) was added to a round-bottom flask containing indolizinone **71** (0.065 g, 0.214 mmol), phenylacetylene (0.049 g, 0.48 mmol), triphenylphosphine (0.008 g, 0.03 mmol), $PdCl_2(PhCN)_2$ (0.005 g, 0.01 mmol), and CuI (0.008 g, 0.04 mmol). This mixture was heated at reflux for 11 h and cooled, and the volatiles were removed by vacuum transfer. The crude material was dissolved in dichloromethane, and washed with 1 N HCl, water, and dilute sodium bicarbonate solution. After drying, the organic phase was removed to give an orange-brown oil. Purification by chromatography and recrystallization produced **75** as light yellow crystals (0.056 g, 94%): mp 120.5–121.5 °C; IR (KBr) 2958, 2205, 1646, 1596, 1593, 1443, 756 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.01 (t, 3, J = 7.3), 1.70 (m, 2), 2.20 (tt, 2, J = 7.4, 7.6), 2.72 (t, 2, J = 7.5), 3.09 (t, 2, J = 7.6), 4.16 (t, 2, J = 7.4), 6.08 (s, 1), 7.33 (m, 3), 7.55 (m, 2); mass spectrum, m/e 277 (M$^+$, 3.92), 262 (5.60), 249 (base, 9.05), 235 (0.90), 178 (1.50), 165 (2.07), 115 (2.02), 77 (2.39).

Anal. Calcd for $C_{19}H_{19}NO$: C, 82.26; H, 6.92; N, 5.05. Found: C, 82.03; H, 6.93; N, 4.95.

2′,3′-Dihydro-6′-(phenylethynyl)-7′-propyl-5′-oxospiro-[1,3-dioxolane-2,1′(5′*H*)-indolizine] (76). To the pyridone **74** (0.061 g, 0.17 mmol) and triphenylphosphine (0.005 g, 0.02 mmol) was added triethylamine (5 mL) and the solution was deoxygenated with nitrogen. $PdCl_2(PhCN)_2$ (0.002 g, 0.005 mmol) was added, and the mixture was heated at reflux for 3 h, at which time TLC showed that starting material had disappeared. The reaction mixture was treated as described for **75** to obtain white needles of **76** (0.54 g, 95%): mp 88–90 °C; IR (KBr) 2953, 2207, 1653, 1649, 1609, 1307, 1225, 1178, 1034, 952, 757 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.02 (t, 3, J = 7.3), 1.72 (qt, 2, J = 7.3, 7.5), 2.37 (t, 2, J = 7.0), 2.76 (t, 2, J = 7.5), 4.15 (m, 6), 6.20 (s, 1), 7.31 (m, 3), 7.54 (m, 2); mass spectrum, m/e 335 (M$^+$, 7.25), 320 (6.88), 307 (base, 11.48), 292 (2.04), 279 (2.13), 220 (1.49), 207 (1.95), 99 (2.36), 55 (2.33).

Anal. Calcd for $C_{21}H_{21}NO_3$: C, 75.19; H, 6.32; N, 4.18. Found: C, 74.96; H, 6.33; N, 4.14.

3-[2′,3′-Dihydro-5′-oxo-7′-(trimethylsilyl)spiro[1,3-dioxolane-2,1′(5′*H*)-indolizin]-6-yl]-2(*E*)-propenoic Acid, Methyl Ester (78). To the pyridone (**73**, 0.391 g, 1.0 mmol) was added $PdCl_2(PhCN)_2$ (0.012 g, 0.03 mmol), triphenylphosphine (0.016 g, 0.06 mmol), methyl acrylate (0.430 g, 5 mmol), and triethylamine (10 mL). The mixture was heated at reflux until TLC analysis showed disappearance of starting material (4 h). After workup and purification by preparative TLC, recrystallization gave yellow needles of **78** (0.324 g, 93%): mp 122–123.5 °C; IR (KBr) 1709, 1649, 1602, 1594, 1281, 1255, 1151 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.40 (s, 9), 2.39 (t, 2, J = 6.8), 3.79 (s, 3), 4.16 (m, 6), 6.41 (s, 1), 7.50 (d, 1, J = 15.4), 7.86 (d, 1, J = 15.4); mass spectrum, m/e 349 (M$^+$, 1.91), 334 (1.89), 290 (base, 32.99), 262 (4.03).

Anal. Calcd for $C_{17}H_{23}NO_5Si$: C, 58.42; H, 6.65; N, 4.01. Found: C, 58.27; H, 6.68; N, 3.90.

3-[2′,3′-Dihydro-5′-oxo-7′-propylspiro[1,3-dioxolane-2,1′-(5′*H*)-indolizin]-6-yl]-2(*E*)-propenoic Acid, Methyl Ester (77). Indolizinone **74** (0.361 g, 1.0 mmol) was treated with methyl acrylate (0.860 g, 10 mmol), triphenylphosphine (0.016 g, 0.06 mmol), and $PdCl_2(PhCN)_2$ (0.012 g, 0.03 mmol) in triethylamine (10 mL) under reflux for 4 h with monitoring by TLC. Purification was performed as described for **78** to produce **77** as white crystals (0.310 g, 97%): mp 140–142 °C; IR (KBr) 2960, 1713, 1696, 1646, 1604, 1587, 1434, 1323, 1275, 1216, 1187, 1037 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.00 (t, 3, J = 7.3), 1.63 (m, 2), 2.38 (t, 2, J = 6.9), 2.70 (t, 2, J = 7.8), 3.78 (s, 3), 4.14 (m, 6), 6.19 (s, 1), 7.52 (d, 1, J = 15.6), 7.77 (d, 1, J = 15.6); mass spectrum, m/e 319 (M$^+$, 2.13),

260 (base, 23.82), 232 (3.21), 160 (3.47).

Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.92; H, 6.64; N, 4.39. Found: C, 64.03; H, 6.64; N, 4.35.

2′,3′-Dihydro-5′-oxo-6′-(2(*E*)-phenylethenyl)-7′-(trimethylsilyl)spiro[1,3-dioxolane-2,1′(5′*H*)-indolizine] (79). Indolizinone **73** (0.392 g, 1.0 mmol), $PdCl_2(PhCN)_2$ (0.012 g, 0.03 mmol), CuI (0.001 g), and triphenylphosphine (0.016 g, 0.06 mmol) were placed in a 25-mL round-bottom flask. Styrene (0.312 g, 3 mmol) was dissolved in 10 mL triethylamine and degassed by using three freeze–pump–thaw cycles. This solution was transferred to the flask, and the mixture was heated at reflux until starting material was consumed (TLC). The reaction mixture was worked up as before and the residue was purified to give yellow crystals of **79** (0.253g, 69%): mp 99–102 °C; IR (KBr) 2965, 1643, 1608, 1590, 1575, 1488, 1314, 1252, 1230, 1198, 1034, 842 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.41 (s, 9), 2.39 (t, 2, J = 7.0), 4.19 (m, 6), 6.41 (s, 1), 7.22 (d, 1, J = 16.0), 7.35 (m, 5), 8.29 (d, 1, J = 16.0); mass spectrum, m/e 367 (M^+, base, 14.72), 352 (1.08), 290 (2.43), 276 (12.32), 99 (3.05), 73 (12.31).

Anal. Calcd for $C_{21}H_{25}NO_3Si$: C, 68.62; H, 6.87; N, 3.81. Found: C, 68.70; H, 6.88; N, 3.83.

Desilylation of this compound with $Me_4NF{\cdot}3H_2O$ following the procedure described for **39** gave a compound with pyridone hydrogen peaks at δ 6.31 (d, 1, J = 7.2) and 7.58 (d, 1, J = 7.2), confirming its structure as **80**.

2′,3′-Dihydro-5′-oxo-7′-propylspiro[1,3-dioxolane-2,1′(5′*H*)-indolizine]-6′-carboxaldehyde (81). Indolizinone **77** (0.190 g, 0.595 mmol) was treated with OsO_4 and $NaIO_4$ as described by Rapoport.[54] Recrystallization of the crude material gave **81** as white crystals (0.135 g, 86%): mp 116.5–118 °C; IR (KBr) 2968, 2942, 2918, 2874, 1680, 1645, 1597, 1530, 1447, 1359, 1319, 1227, 1211 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$), δ 1.01 (t, 3, J = 7.3), 1.60 (m, 2), 2.41 (t, 2, J = 6.8), 2.94 (m, 2), 4.14 (t, 2, J = 6.8), 4.17 (m, 4), 6.15 (s, 1), 10.51 (s, 1); mass spectrum, m/e 263 (M^+, 1.16), 235 (0.87), 220 (3.46), 207 (base, 25.70), 192 (0.84), 179 (3.54).

Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.85; H, 6.52; N, 5.32. Found: C, 63.69; H, 6.49; N, 5.20.

From the alcohol **82**: indolizinone alcohol **82** (obtained from **59**, 0.051 g, 0.19 mmol) and MnO_2 (0.087 g, 1.0 mmol) were allowed to react in dichloromethane at reflux for several hours. At the end of this time more MnO_2 was added (0.087 g, 1.0 mmol), and the mixture was heated again at reflux. This procedure was repeated every 2 h until TLC analysis showed that no starting material remained. The cooled reaction mixture was filtered through Celite, and the solvent was removed by rotary evaporation. Recrystallization afforded the aldehyde **81** (0.047 g, 94%).

2′,3′-Dihydro-6′-(hydroxymethyl)-5′-oxo-7′-propylspiro-[1,3-dioxolane-2,1′(5′*H*)-indolizine] (82). To the aldehyde **81** (0.198 g, 0.75 mmol) in ethanol at 0 °C was added sodium borohydride (0.038 g, 1.0 mmol) in portions with stirring. The solution was warmed to room temperature, worked up with water, and extracted with dichloromethane. The resulting solid was recrystallized to give white crystals of **82** (0.174 g, 87%): mp 112–114 °C; IR (KBr) 3314, 1651, 1584, 1576, 1316, 1207, 1032 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.96 (t, 3, J = 7.3), 1.57 (m, 2), 2.78 (t, 2, J = 6.9), 2.53 (m, 2), 4.14 (m, 6), 4.36 (t, 1, J = 6.4), 4.65 (d, 2, J = 6.4), 6.16 (s, 1); mass spectrum, m/e 265 (M^+, base, 13.01), 247 (5.39), 236 (5.65), 232 (7.91), 219 (6.62).

Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.23; N, 5.28. Found: C, 63.15; H, 7.25; N, 5.25.

2′,3′-Dihydro-6′-cyano-5′-oxo-7′-propylspiro[1,3-dioxolane-2,1′(5′*H*)-indolizine] (84). Conversion of the aldehyde **81** (0.078 g, 0.30 mmol) to the nitrile was performed as described by Sosnovsky.[61] Purification by preparative TLC, followed by recrystallization gave **84** as a white solid (0.062 g, 80%): mp 134–135 °C; IR (KBr) 2220, 1659, 1606, 1533, 1346, 1199, 1032 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.02 (t, 3, J = 7.3), 1.71 (m, 2), 2.40 (t, 2, J = 6.9), 2.73 (t, 2, J = 7.7), 4.13 (t, 2, J = 7.1), 4.17 (m, 4), 6.19 (s, 1); mass spectrum, m/e 260 (M^+, 9.28), 232 (2.17), 188 (5.38), 99 (base, 16.34).

Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.59; H, 6.21; N, 10.76. Found: C, 64.47; H, 6.27; N, 10.64.

6′-Cyano-α-ethyl-2′,3′-dihydro-5′-oxospiro[1,3-dioxolane-2,1′(5′*H*)-indolizine]-7′-acetic Acid, Ethyl Ester (85). Following reported procedures,[59] to NaH (washed with hexane, 0.043 g, 1.79 mmol) in toluene was added pyridone **84** (0.048 g, 0.184 mmol) and the mixture was heated to reflux. Diethyl carbonate (0.059 g, 0.5 mmol) and ethanol (0.002 g, 0.05 mmol) in toluene were added to the boiling solution through the top of the condenser. The mixture turned orange-brown, and a dark brown precipitate formed. After 4 h, the cooled reaction mixture was poured into cold dilute HCl. The aqueous layer was extracted several times with ether and dichloromethane, and the organic phases were combined, dried, and evaporated to an oil. Purification by preparative TLC (ethyl acetate/methanol, 1:1) followed by recrystallization afforded **85** as a white solid (0.020 g, 32%): mp 99–110 °C (lit.[59] mp 121–122 °C, lit.[58] mp 126–127 °C); IR (KBr) 2227, 1736, 1662, 1612 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.97 (t, 3, J = 7.4), 1.26 (t, 3, J = 7.2), 1.80 (m, 1), 2.09 (m, 1), 2.41 (t, 2, J = 6.8), 3.93 (t, 1, J = 7.6), 4.15 (m, 8), 6.41 (s, 1); mass spectrum, m/e 332 (M^+, 10.80), 300 (2.15), 285 (6.85), 260 (6.52), 245 (6.34), 99 (base, 21.36).

2′,3′-Dihydro-α-ethyl-5′-oxospiro[1,3-dioxolane-2,1′-(5′*H*)-indolizine]-7′-acetic Acid, Ethyl Ester (86). To KH (washed with hexane, 1.294 g, 32.26 mmol) in toluene (10 mL) was added the pyridone **57** (0.442 g, 1.44 mmol) in toluene. The mixture was heated to reflux for 10 min, then diethyl carbonate (0.510 g, 4.32 mmol) and ethanol (0.018 g, 0.4 mmol) in toluene were added via syringe, and the mixture was worked up as in the preparation of **85**. Purification of the resulting oil by preparative TLC produced **86** as a colorless oil (0.239 g, 54%): IR (neat) 2973, 1732, 1672, 1604, 1314, 1246, 1184, 1037 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.91 (t, 3, J = 7.4), 1.24 (t, 3, J = 7.1), 1.77 (m, 1), 2.00 (m, 1), 2.38 (t, 2, J = 6.9), 3.30 (t, 1, J = 7.6), 4.17 (m, 8), 6.27 (d, 1, J = 1.3), 6.60 (d, 1, J = 1.3); mass spectrum, m/e 307 (M^+, base, 4.98), 279 (1.16), 234 (2.10), 207 (1.74), 190 (2.07), 99 (4.18); exact mass calcd for $C_{16}H_{21}NO_5$ 307.1419, found 307.1414.

1,5-Dioxo-α-ethyl-1,2,3,5-tetrahydroindolizine-7-acetic Acid, Ethyl Ester (87). The ketal **86** (0.240 g, 0.781 mmol) and oxalic acid dihydrate (0.100 g, 0.8 mmol) in 30 mL ethanol/water (1:2) were heated to 80 °C for 1 h. The cooled solution was extracted with chloroform, and the organic layer was washed with dilute aqueous sodium bicarbonate. The resulting oil was purified by preparative TLC to give **75** as a colorless oil (0.154 g, 75%): IR (neat) 1741, 1662, 1601 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.92 (t, 3, J = 7.4), 1.24 (t, 3, J = 7.1), 1.75 (m, 1), 2.04 (m, 1), 2.92 (t, 2, J = 6.8), 3.39 (t, 1, J = 7.6), 4.13 (m, 2), 4.29 (t, 2, J = 6.8), 6.75 (d, 1, J = 1.5), 6.90 (d, 1, J = 1.5); mass spectrum, m/e 263 (M^+, base, 9.06), 235 (2.25), 190 (6.82), 148 (1.77); exact mass calcd for $C_{14}H_{17}NO_4$ 263.1157, found 263.1150.

9,11-Dihydro-α-ethyl-9-oxoindolizino[1,2-*b*]quinoline-7-acetic Acid, Ethyl Ester (88). When the procedure of Rapoport[62] was followed, ketone **87** (0.150 g, 0.57 mmol) was allowed to react with *N*-(2-aminobenzylidene)-*p*-toluidine (0.173 g, 0.82 mmol) in boiling toluene containing a catalytic amount of *p*-toluenesulfonic acid. Purification by preparative TLC, followed by recrystallization gave **88** as a light yellow solid (0.155 g, 78%): mp 192–194 °C; IR (KBr) 1735, 1660, 1619, 1600 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.97 (t, 3, J = 7.3), 1.26 (t, 3, J = 7.1), 1.94 (m, 1), 2.17 (m, 1), 3.47 (t, 1, J = 7.7), 4.18 (m, 2), 5.25 (s, 2), 6.66 (d, 1, J = 1.4), 7.35 (d, 1, J = 1.4), 7.64 (dt, 1, J = 1.3, 7.5), 7.81 (dt, 1, J = 1.3, 7.5), 7.92 (d, 1, J = 8.0), 8.21 (d, 1, J = 8.5), 8.36 (s, 1); mass spectrum, m/e 348 (M^+, base, 4.54), 320 (0.92), 275 (2.90), 248 (2.12).

Anal. Calcd for $C_{21}H_{20}N_2O_3$: C, 72.38; H, 5.80; N, 8.04. Found: C, 72.29; H, 5.84; N, 8.03.

The ethyl ester was treated with sodium methoxide in methanol to produce methyl ester **49** quantitatively. Recrystallization from ethyl acetate afforded pale yellow crystals: mp 210–211 °C (lit.[41a] mp 198–200 °C, lit.[65] mp 229–230 °C, lit.[73] mp 209–211 °C, lit.[74] mp 201–203 °C); IR (KBr) 1738, 1660, 1620, 1601 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.97 (t, 3, J = 7.3), 1.92 (m, 1), 2.18 (m, 1), 3.49 (t, 1, J = 7.6), 3.72 (s, 3), 6.65 (d, 1, J = 1.1), 7.33 (d, 1, J = 1.1), 7.65 (dt, 1, J = 1.3, 7.5), 7.82 (dt, 1, J = 1.3, 7.5), 7.93 (d, 1, J = 8.1), 8.22 (d, 1, J = 8.4), 8.37 (s, 1).

Anal. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.83; H, 5.44; N, 8.38. Found: C, 71.52; H, 5.44; N, 8.16.

The spectral characteristics of this compound matched exactly those reported previously.[73,74]

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Registry No. (±)-**1**, 31456-25-4; **3**, 12078-25-0; **4**, 871-84-1; **5**, 103-71-9; **6**, 92957-80-7; **7**, 2396-63-6; **8**, 1943-82-4; **9**, 92957-81-8; **10**, 1295-35-8; **11**, 622-76-4; **12**, 92957-82-9; **13**, 92957-83-0; **14**, 92957-84-1; **26a**, 88761-58-4; **26b**, 88761-62-0; **27a**, 14630-40-1; **27b**, 18270-17-2; **27c**, 88761-61-9; **27c** (ketone), 18387-58-1; **27d**, 14630-42-3; **27e**, 35792-10-0; **27e** (ketone), 1679-36-3; **27f**, 88761-60-8; **27g**, 4341-76-8; **28**, 53293-00-8; **29**, 55183-45-4; **30**, 88761-32-4; **31**, 88761-33-5; **32**, 88761-35-7; **33**, 88761-42-6; **34**, 92957-85-2; **35**, 92957-86-3; **36**, 88761-43-7; **37**, 88761-44-8; **38**, 92957-88-5; **39**, 92957-89-6; **40**, 92958-08-2; **41**, 92957-91-0; **42**, 92957-87-4; **49**, 63281-84-5; **51**, 1490-25-1; **52**, 88761-59-5; **53**, 92958-07-1; **55**, 92957-90-9; **56**, 88761-45-9; **57**, 88761-48-2; **58**, 88761-49-3; **59**, 88761-51-7; **60**, 88761-50-6; **61**, 50478-69-8; **62**, 88761-54-0; **63**, 92957-92-1; **64**, 92957-93-2; **65**, 92957-94-3; **66**, 88761-36-8; **67**, 92957-95-4; **68**, 92957-96-5; **69**, 92957-97-6; **70**, 88761-39-1; **71**, 88761-37-9; **72**, 92957-98-7; **73**, 88761-47-1; **74**, 88761-46-0; **75**, 92957-99-8; **76**, 88761-53-9; **77**, 88761-56-2; **78**, 88761-55-1; **79**, 88761-52-8; **80**, 92958-00-4; **81**, 92958-01-5; **82**, 92958-02-6; **84**, 92958-03-7; **85**, 64389-33-9; **86**, 92958-04-8; **87**, 92958-05-9; **88**, 92958-06-0; $HC{\equiv}C(CH_2)_4OH$, 928-90-5; *t*-BuC≡CH, 917-92-0; Me_3SiCl, 75-77-4; *n*-PrC≡CCH_2OH, 764-60-3; TBDPSCl, 58479-61-1; $CH_2{=}N(CH_3)_2{}^+Cl^-$, 30354-18-8; PhC≡CH, 536-74-3; CuI, 7681-65-4; $PdCl_2(PhCN)_2$, 14420-64-5; $CH_2{=}CHCO_2Me$, 96-33-3; $PhCH{=}CH_2$, 100-42-5; $(EtO)_2CO$, 105-58-8; *N*-(2-aminobenzylidene)-*p*-toluidine, 55857-35-7.

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Utility of *p*-Nitrophenyl 3-Bromo-2,2-diethoxypropionate (NPBDP) in Heterocyclic Synthesis

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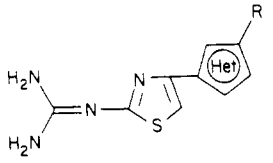
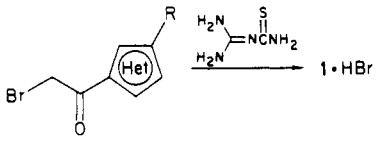
p-Nitrophenyl 3-bromo-2,2-diethoxypropionate (NPBDP, **3**) reacts with a variety of nucleophiles at the activated ester to afford the corresponding 3-bromo-2,2-diethoxypropionylated derivatives. With bifunctional nucleophiles, propionylation can be followed by intramolecular cyclization to give cyclic products. The α-bromo ketone moiety of the propionylated derivative can be liberated by heating at 85 °C in 95% formic acid. The utility of NPBDP in the synthesis of highly functionalized small molecules, as well as heterocycles, is presented.

Work from these laboratories designed to discover novel therapeutic agents led to the identification of an interesting series of 2-guanidino-4-(heteroaryl)thiazoles of general structure **1**, in which the heteroaryl ring was a five-membered nitrogen containing ring. The original syntheses of **1** were cumbersome, in that they were based on building a heterocycle onto a preformed 2-guanidinothiazole moiety. While this approach proved suitable for the initial targets, the preparation of other derivatives of interest was difficult because of the general insolubility of guanidinothiazoles, a characteristic attributable to their propensity for hydrogen bonding.

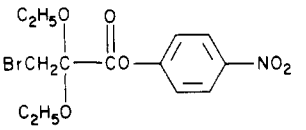


1

Pursuant to the activity of **1**, it was of interest to prepare compounds in which the heteroaryl ring was a 5-(1,2,4-oxadiazolyl) and 5-(1,2,4-thiadiazolyl) moiety. It was also desirable to replace the 2-guanidinothiazole with a 5-guanidino-1,2,4-oxadiazole. Both of these goals were either difficult or precluded by the original synthesis, and thus, an alternate scheme was necessary. A route that was especially appealing involved forming the 2-guanidinothiazole moiety in the last step so that the very characteristics which cause the insolubility of these compounds could be used to facilitate their isolation in pure form. However, in order for such a scheme to be successful, a simple synthesis of the appropriate 2-halo-1-heteroaryl-1-ethanones (**2**) was necessary. This paper details reactions of *p*-nitrophenyl 3-bromo-2,2-diethoxypropionate (NPBDP, **3**), a reagent which proved to be ideally suited to the preparation of these key ethanones. Also presented are reactions that demonstrate the utility of NPBDP, not only in heterocyclic synthesis but also in the synthesis of highly functionalized small molecules.[1]



2



NPBDP

3

The necessity of a reagent such as NPBDP for these purposes is best demonstrated by the initial unsuccessful attempts at preparing a 5-(1,2,4-oxadiazolyl) analogue of **1**. This approach was based on recent chemistry developed by Lin et al.[2] Ethyl pyruvate was converted to ketal **4**, which, when treated with ammonium hydroxide, gave 2,2-diethoxypropionamide (**5**). Reaction of **5** with dimethylacetamide dimethyl acetal readily gave amidine **6**, which, upon reaction with hydroxylamine followed by

(1) For a preliminary account of this work, see: LaMattina, J. L.; Mularski, C. J. *Tetrahedron Lett.*, **1983**, 2059.
(2) Lin, Y.; Lang, S. A., Jr.; Lovell, M. F.; Perkinson, N. A. *J. Org. Chem.* **1979**, *44*, 4160.

0022-3263/84/1949-4800$01.50/0