Approaches to the Synthesis of (±)-Strychnine via the Cobalt-Mediated [2 + 2 + 2] Cycloaddition: Rapid Assembly of a Classic Framework

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Abstract: Five synthetic approaches to racemic strychnine (**1**), with the cobalt-mediated [2 + 2 + 2] cycloaddition of alkynes to indoles as the key step, are described. These include the generation and attempted cyclization of macrocycle **8** and the synthesis of dihydrocarbazoles **15**, **22**, and **26** and their elaboration to pentacyclic structures via a conjugate addition, dipolar cycloaddition, and propellane-to-spirofused skeletal rearrangement, respectively. Finally, the successful total synthesis of **1** is discussed. The development of a short, highly convergent route (14 steps in the longest linear sequence) is highlighted by the cyclization of enynoylindole **40** with acetylene and the formal intramolecular 1,8-conjugate addition of amine **49** to form pentacycle **50**. Numerous attempts toward the formation of the piperidine ring of **1** from vinyl iodide **56** were made and its successful formation via palladium-, nickel-, and radical-mediated processes is described.

Introduction

Strychnine (**1**, Figure 1), the infamous poisonous alkaloid, has been known to man for thousands of years, and to Western medicine since the sixteenth century. Although in the past it has found application as a mild stimulatory tonic and appetite enhancer, its most common uses today are as a rodenticide and animal stimulant. Isolated in quantity from the Southeast Asian *Strychnos nux-vomica* and *Strychnos ignatii*, in which the alkaloid is present in as much as 1.5−2%, strychnine toxicity arises from the blocking of postsynaptic inhibition in the spinal cord and lower brain stem where it acts as a competitive ligand at the neuronal receptor for glycine, an inhibitory neurotransmitter.[1] As a high-affinity and highly selective antagonist, the alkaloid has been useful as a tool for the structural characterization of this receptor, as well as in numerous biochemical studies of the nervous system.[2] For an adult human, a lethal dose of strychnine is in the range of 100−300 mg. Death is caused by asphyxiation, a result of the intense convulsions induced by acoustic, tactile, or visual stimuli and the subsequent respiratory paralysis.[3]

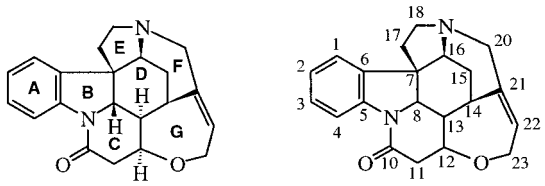

Figure 1. The strychnine (**1**) structure with numbering and ring labeling used throughout this paper.

Strychnine holds a special place in the history of organic chemistry. First isolated in 1818, it was one of the first alkaloids to be obtained in pure form.[4] The pursuit of its molecular structure presented a formidable challenge for classical degradative strategies and lasted more than 60 years, resulting in the publication of hundreds of papers and communications.[5] The experimental work of Leuchs and Robinson stands out as the most notable among these,[6] and it was the latter who, in 1946, proposed the correct structure for strychnine.[7] In the following year, Woodward independently suggested the same framework.[8] This accomplishment signaled the culmination and the end of the era of classical structure elucidation. Only four years later, final confirmation of the structure of **1** was obtained by X-ray crystallography.[9]

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(1) Aprison, M. H. In *Glycine Neurotransmission*; Otterson, O. P., Strom-Mathisen, J., Eds.; Wiley: New York, 1990; pp 1−23.
(2) For recent reviews see: (a) Chebib, M.; Johnston, G. A. R. *Clin. Exp. Pharmacol. Physiol.* **1999**, *26*, 937. (b) Breitinger, H. G.; Becker, C. M. *Curr. Pharmacol. Des.* **1998**, *4*, 315. (c) Béchade, C.; Sur, C.; Triller, A. *Bioessays* **1994**, *16*, 735.
(3) Klaassen, C. D. In *The Pharmacological Basis of Therapeutics*, 9th ed.; Hardman, J. G., Limbid, L. E., Eds.; McGraw-Hill: New York, 1995; pp 1689−1690.
(4) (a) Pelletier, P. J.; Caventou, J. B. *Ann. Chim. Phys.* **1818**, *8*, 323. (b) Pelletier, P. J.; Caventou, J. B. *Ann. Chim. Phys.* **1819**, *810*, 142.
(5) For a review, see: Smith, G. F. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1965; Vol. 8, pp 591−671.
(6) (a) Leuchs, H. *Ber. Dtsch. Chem. Ges.* **1939**, *72*, 1588. (b) Briggs, L. H.; Openshaw, H. T.; Robinson, R. J. *J. Chem. Soc.* **1946**, 903.
(7) Openshaw, H. T.; Robinson, R. J. *Nature* **1946**, *157*, 438.
(8) (a) Woodward, R. B.; Brehm, W. J. *J. Am. Chem. Soc.* **1948**, *70*, 2107. (b) Woodward, R. B.; Brehm, W. J.; Nelson, A. L. *J. Am. Chem. Soc.* **1947**, *69*, 2250.
(9) (a) Robertson, J. H.; Beevers, C. A. *Acta Crystallogr.* **1951**, *4*, 270. (b) Bokhoven, C.; Schoone, J. C.; Bijovet, J. M. *Acta Crystallogr.* **1951**, *4*, 275. (c) Peerdemann, A. F. *Acta Crystallogr.* **1956**, *9*, 824.

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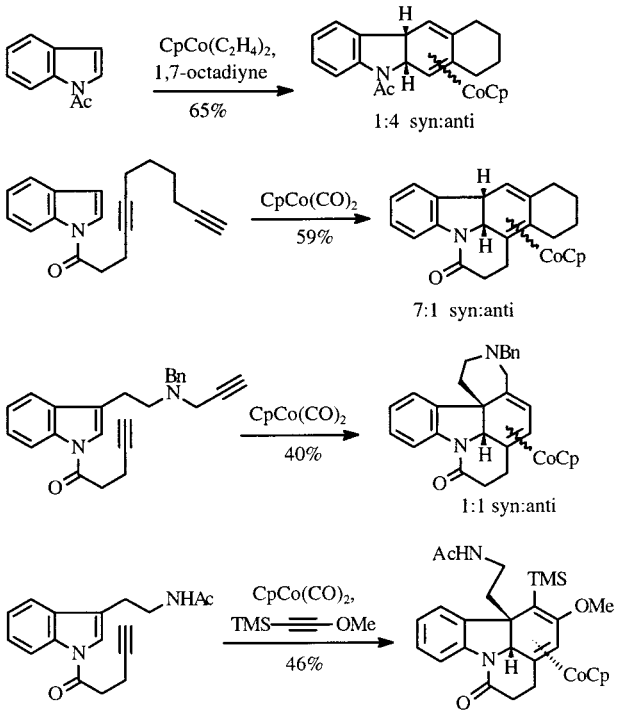
When Woodward began his total synthesis of strychnine in 1948, the construction of a molecule of such complexity had never before been undertaken. Its completion in 1954 remains a landmark in organic chemistry and helped usher in the era of modern organic synthesis.[10] The challenge posed by the molecule, with its seven rings and six stereocenters displayed across a framework of only 24 atoms, combined with its historical significance, has resulted in the continued attraction of the alkaloid as a synthetic target. Remarkably, nearly 40 years elapsed before Woodward's seminal achievement was equaled, with the report of numerous syntheses within the last 10 years.[11] These include the relay total synthesis of (−)-strychnine by Magnus;[12] the asymmetric total syntheses by Overman,[13] Kuehne,[14] and Bosch;[15] and the assembly of the racemic form by Kuehne,[16] Rawal,[17] Stork,[18] Martin,[11a,19] and our laboratory.[20] Here we offer a complete description of our efforts toward the synthesis of **1** employing a cobalt-mediated [2 + 2 + 2] cycloaddition reaction and the ultimate development of a successful approach. [21]

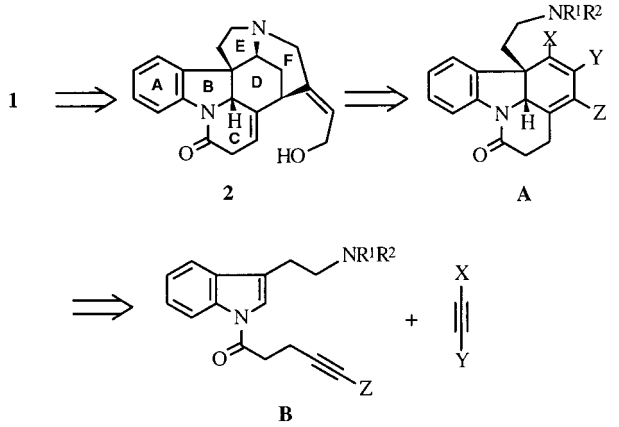
The Cobalt Way to Strychnine

The cobalt-mediated [2 + 2 + 2] cycloaddition has proven to be a powerful tool for the construction of complex, polycyclic molecules. The ability of cyclopentadienylcobalt to effect the cyclization of three unsaturated functionalities with a high degree of chemo-, regio-, and stereoselectivity has resulted in the synthesis of several complex natural[22] and unnatural[23] products. Among the wide variety of unsaturated functionalities which participate in this reaction are a number of aromatic heterocyclic double bonds, such as those in pyrrole,[24a] imidazole,[24b] thiophene, furan,[24c] and benzofuran.[24d] The indole nucleus is also active in these cyclizations, as exemplified by the selections in Scheme 1.[25] Indoles, including those substituted at C3, can be cyclized both intra- and intermolecularly. Additionally, a wide variety of functionalized alkynes can participate in the reaction, often with a high degree of regioselectivity. Finally, the cyclizations give the cis orientation of the H and R substituents at C2 and C3. Consideration of **1** as a multiply fused indole derivative suggested the application of the cobalt-mediated [2 + 2 + 2] cycloaddition as a unique entry into the strychnine framework.

Scheme 1. Cobalt-Mediated [2 + 2 + 2] Cycloadditions to Indoles



Scheme 2. Retrosynthetic Analysis of a Cobalt-Mediated Approach to **1** from *N*-(4-Pentynoyl)indoles



In our proposed approach (Scheme 2), the partly intramolecular cyclization of *N*-(4-pentynoyl)indole derivatives B would furnish a dihydrocarbazole system A constituting the A,B,C,D frame of **1**. Construction of the E ring was envisaged to involve nucleophilic attack of the nitrogen on the D ring diene unit. Ring F was thought to be accessible by a transition metal catalyzed coupling of an appropriately functionalized *N*-alkenyl function, thus providing the strychnine derivative, isostrychnine (**2**). Closure of the final ring would then proceed through the

(10) (a) Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. J. *J. Am. Chem. Soc.* **1954**, *76*, 4749.(b) Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. J. *Tetrahedron* **1963**, *19*, 247. (c) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinheim, 1996; pp 21−40.

(11) For reviews see: (a) Bonjoch, J.; Sole, D. *Chem. Rev.* **2000**, *100*, 3455. (b) Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1144.

(12) Magnus, P.; Giles, M.; Bonnert, R.; Johnson, G.; McQuire, L.; Deluca, M.; Merritt, A.; Kim, C. S.; Vicker, N. *J. Am. Chem. Soc.* **1993**, *115*, 8116.

(13) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1995**, *117*, 5776.

(14) Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1998**, *63*, 9427.

(15) Solé, D.; Bonjoch, J.; García-Rubio, S.; Peidró, E.; Bosch, J. *Chem. Eur. J.* **2000**, *6*, 655.

(16) Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1993**, *58*, 7490.

(17) Rawal, V. H.; Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685.

(18) Stork, G. Reported at the Ischia Advanced School of Organic Chemistry, Ischia Porto, Italy, September 21, 1992.

(19) Martin, S. F.; Clark, C. W.; Ito, M.; Mortimore, M. *J. Am. Chem. Soc.* **1996**, *118*, 9804.

(20) Eichberg, M. J.; Dorta, R. L.; Lamottke, K.; Vollhardt, K. P. C. *Org. Lett.* **2000**, *2*, 2479.

(21) Some of this work has appeared as preliminary communications: (a) Grotjahn, D. B.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1990**, *112*, 5653. (b) Reference 20.

(22) Saa, C.; Crotts, D. D.; Hsu, G.; Vollhardt, K. P. C. *Synlett* **1994**, 487 and references therein.

(23) Vollhardt, K. P. C.; Mohler, D. L. *Advances in Strain in Organic Chemistry*; JAI Press: Greenwich, CT, 1996; Vol. 5, pp 121−160.

(24) (a) Sheppard, G. S.; Vollhardt, K. P. C. *J. Org. Chem.* **1986**, *51*, 5496. (b) Boese, R.; Knölker, H. J.; Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1035. (c) Boese, R.; Harvey, D. F.; Malaska, M. J.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1994**, *116*, 11153. (d) Pérez, D.; Siesel, B. A.; Malaska, M. J.; David, E.; Vollhardt, K. P. C. *Synlett* **2000**, 366. (e) Pelissier, H.; Rodriguez, J.; Vollhardt, K. P. C. *Chem. Eur. J.* **1999**, *5*, 3549.

(25) (a) Grotjahn, D. B.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1986**, *108*, 2091. (b) Boese, R.; Van Sickle, A. P.; Vollhardt, K. P. C. *Synthesis* **1994**, 1374.

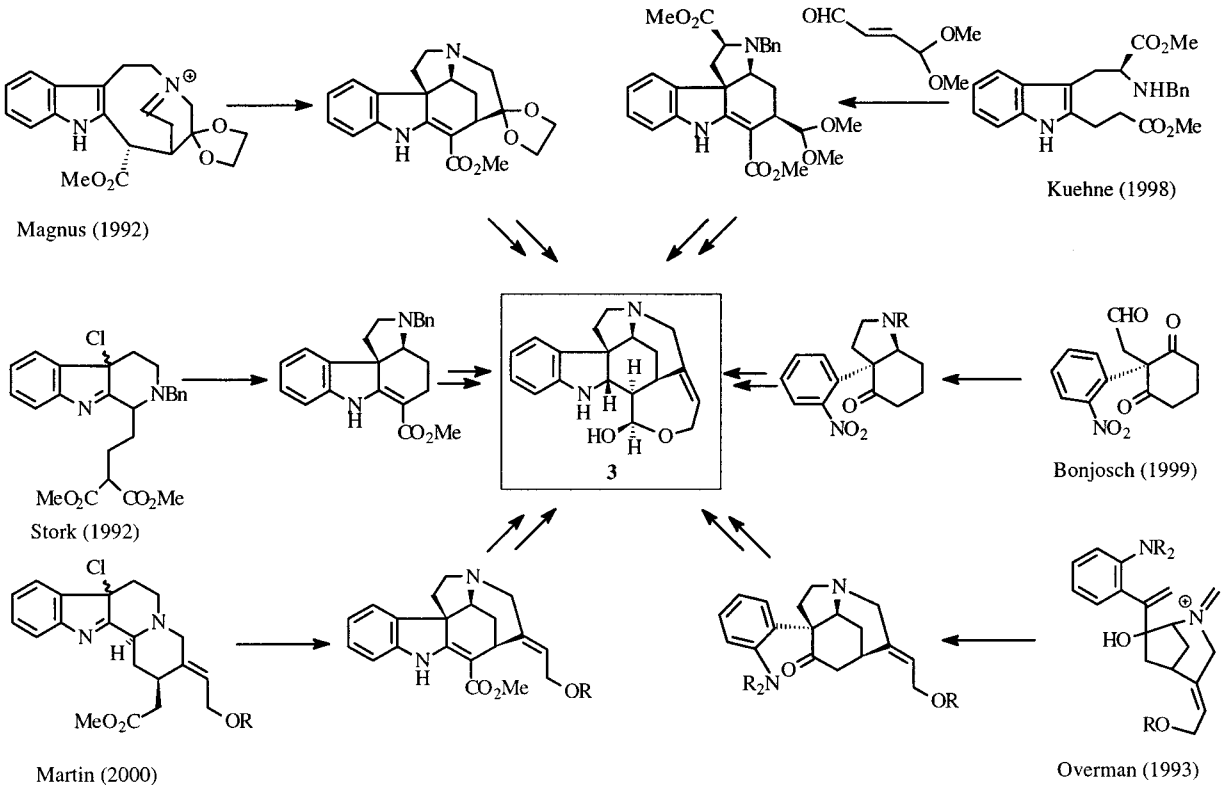
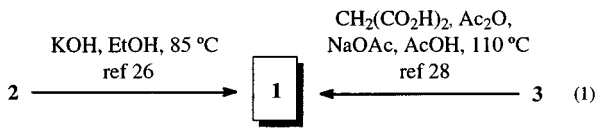


Figure 2. Synthetic approaches to E ring and the Wieland−Gumlich aldehyde (**3**).

well-known isostrychnine−strychnine isomerization (eq 1).[26,27]



The strategy described here presents a previously unexplored approach to the strychnine heptacycle. Not only does the early formation of the tetrahydropyridone ring C differ fundamentally from those routes which culminate in the conversion of the Wieland−Gumlich aldehyde (**3**) to **1**[28,29] (Figure 2, eq 1), but also a cobalt-mediated ring assembly presents a topologically novel entry into the isostrychnine system when compared to other syntheses (Figure 3). The establishment of the C7 quaternary center, which in most syntheses is associated with formation of the pyrrolidine E ring, is a crucial step in the synthesis of **1**. Whereas Bosch and co-workers used a Claisen rearrangement to solve this problem, and the groups of Martin and Stork both applied a base-catalyzed skeletal rearrangement, most strategies have utilized an intermediate imine species to form the necessary carbon−carbon bond. Apart from our approach, only Rawal has addressed this issue through a cycloaddition reaction by employing the classical [4 + 2] process.

The AB → ABCD → ABCDEF Approach to 1

In a first attempt to implement the general strategy of Scheme 2, we envisioned the cyclization of **5** with an appropriate alkyne leading to an ABCD intermediate **4** (Scheme 3). Subsequent manipulation might eventually lead to **2** and hence **1**. The attractions of this strategy were the early control of the stereochemistry at C21−C22 and the similarly early installation of the C14−C21 connection.

To investigate the feasibility of this cyclization, the model system **8** was chosen (Scheme 4). Tryptamine was alkylated with commercially available 2,3-dibromo-1-propene to afford **6** in 59% yield. After protection of the amine function as a carbamate,[30] the indole nitrogen was acylated with 4-pentynoyl chloride,[31] giving **7** in 50% yield.[32] Finally, intramolecular coupling was achieved using palladium and Cu(I) in triethylamine under high dilution conditions.[33] Attempts to improve the moderate yields of **8** (27%) by variation of reaction temperature or concentration of the substrate were unsuccessful.

Unfortunately, upon exposure to 1-methoxy-2-trimethylsilylethyne (**9**) in the presence of $CpCo(CO)_2$ in refluxing *m*-xylene, **8** gave cyclobutadiene complexes **11** as a 12:1 mixture of regioisomers in 64% overall yield. The incorporation of the alkyne cocyclization partner **9** and cyclopentadienyl cobalt was evident from the electron-impact MS ($M^+ = 630$) and ^{1}H NMR spectrum, which displayed trimethylsilyl peaks at δ 0.20 (s, 9H) and 0.23 (s, 9H) ppm, methoxy signals at δ 3.59 (s, 3H) and

(26) Prelog, V.; Battegay, J.; Taylor, W. I. *Helv. Chim. Acta* **1948**, *31*, 2244.

(27) Formation of **2** from **1**: Leuchs, H.; Schulte, H. *Chem. Ber.* **1942**, *75*, 1522.

(28) Anet, F. A. L.; Robinson, R. *Chem. Ind.* **1953**, 245.

(29) Formation of **3** from **1**: (a) Wieland, H.; Gumlich, W. *Liebigs Ann. Chem.* **1932**, *494*, 191. (b) Wieland, H.; Kaziro, K. *Liebigs Ann. Chem.* **1933**, *506*, 60. (c) Anet, F. A. L.; Robinson, R. *J. Chem. Soc.* **1955**, 2253. (d) Hymon, J. R.; Schmid, H.; Karrer, P.; Boller, A.; Els, H.; Fahrni, P.; Fürst, A. *Helv. Chim. Acta* **1969**, *52*, 1564. (e) Szabo, L.; Clauder, O. *Acta Chim. Acad. Sci. Hung.* **1977**, *95*, 85. (f) Kapoor, V. K.; Sharma, S. K.; Chagti, K. K.; Singh, M. *Ind. J. Chem.* **1988**, *27B*, 641.

(30) Carpino, L. A. *Acc. Chem. Res.* **1973**, *6*, 191.

(31) (a) Schulte, K. E.; Reisch, J. *Arch. Pharm. (Weinheim, Ger.)* **1959**, *292*, 51. (b) Prepared by a modification of the method for 5-hexanoyl chloride reported in: Earl, R. A.; Vollhardt, K. P. C. *J. Org. Chem.* **1984**, *49*, 4786.

(32) Kikugawa, Y. *Synthesis* **1981**, 460.

(33) (a) Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1990; Vol. 3, p 521. (b) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627. (c) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *15*, 4467.

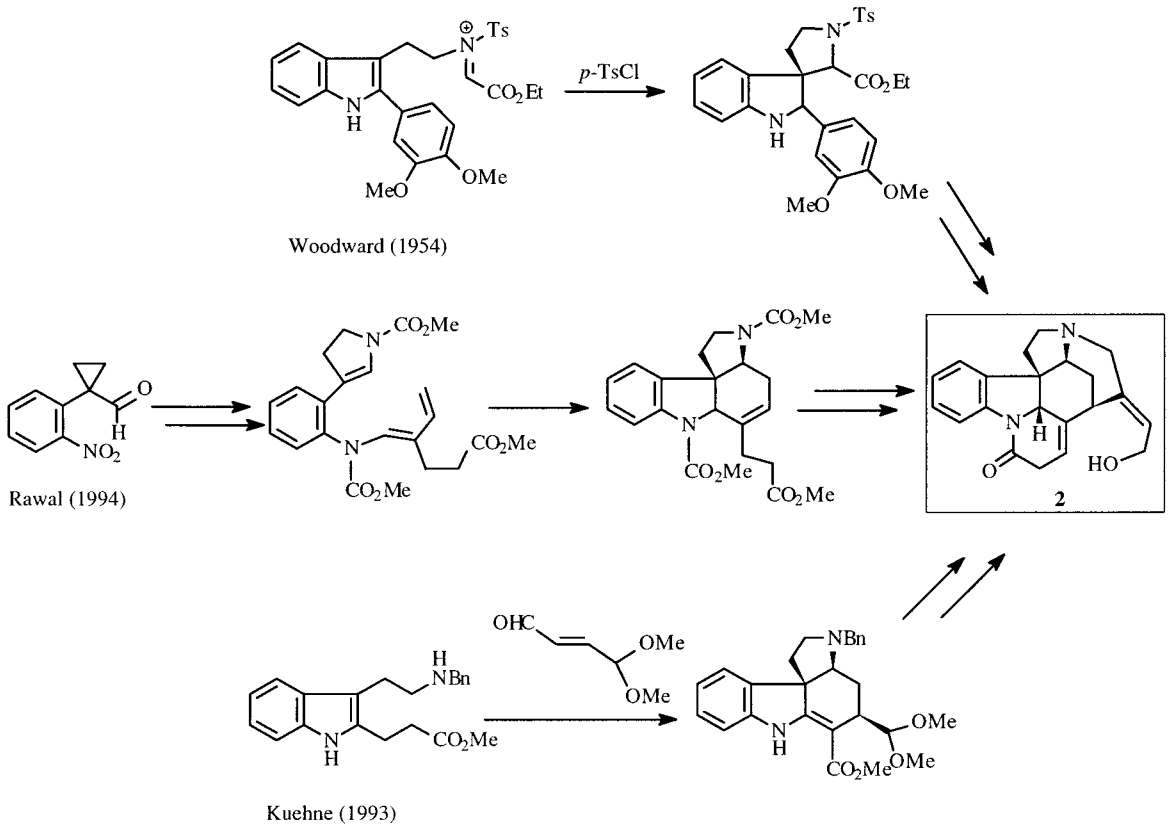
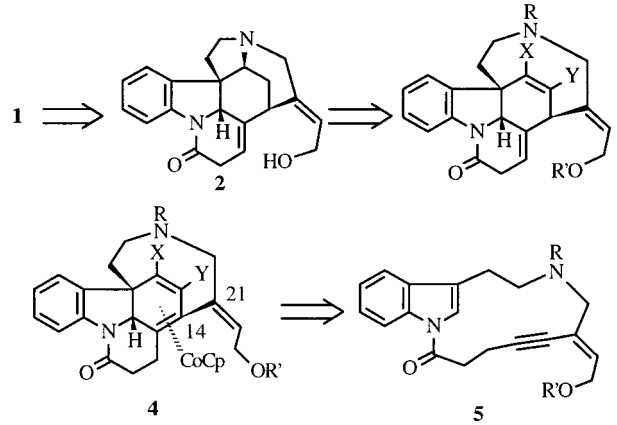


Figure 3. Synthetic approaches to isostrychnine (**2**).

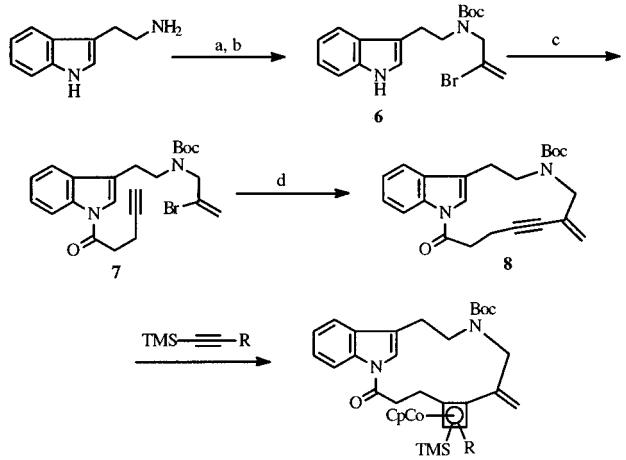
Scheme 3. Synthetic Approach to **1** via a [2 + 2 + 2] Cycloaddition of Macrocycle **5**



3.48 (s, 3H) ppm, and Cp absorptions at δ 4.73 (s, 5H) and 4.75 (s, 5H) ppm for the major and minor isomers, respectively. Corresponding resonances for the aromatic pyrrole at δ 7.06 (s, 1H) and 7.14 (s, 1H) ppm indicated that the aromatic indole nucleus was still intact. The regiochemistry of the two isomers could not be assigned using 1D or 2D NOE experiments. The exclusive formation of **11** was disappointing, considering that **9** had typically been an excellent [2 + 2 + 2] cocyclization partner in *N*-(4-pentynoyl)indole cyclizations.[25a]

Variation of the reaction conditions in an attempt to favor addition to the indole system was unsuccessful. In analogous cyclizations, it was found that lowering the reaction temperature increased the yield of the six-membered-ring relative to the four-membered-ring product.[24a] However, reaction of **8** at room temperature using $CpCo(C_2H_4)_2$[34] gave again only **11** (29%), in addition to unreacted starting material (19%). Use of another cocyclization partner, namely acetylenic ester **10**, generated

Scheme 4. Synthesis and Cyclization of Model Macrocycle **8**[a]



[a] Conditions: (a) 2,3-dibromo-1-propene (0.5 equiv), toluene, 111 °C, 1.75 h, 59%; (b) $(t\text{-BuO}_2C)_2O$ (1 equiv), CH_2Cl_2, room temperature, 1 h, 87%; (c) i. KOH, glyme, room temperature, 15 min; ii. 4-pentynoyl chloride (1.5 equiv), glyme, 0 °C, 1 min, 50%; (d) $Pd(PPh_3)_2Cl_2$ (2.5 mol %), CuI (5 mol %), $HNEt_2$, 55 °C, 24 h, 27%.

cyclobutadiene **12** as a single isomer of unknown configuration in 40% yield. The failure of **8** to undergo [2 + 2 + 2] cycloaddition could originate from a metallacyclopentadiene intermediate (see, e.g., Scheme 13) too strained to coordinate and insert the enamine double bond of the indole moiety. Alternatively, preferential formation of the undesired metallacyclopentadiene regioisomer, placing the vinyl substituent α to

(34) Jonas, K.; Deffense, E.; Habermann, D. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 716.

the cobalt, would preclude the desired insertion. In either case, formal reductive elimination to form the cyclobutadiene complex is the most favored alternative pathway. In view of these difficulties, the macrocycle approach was abandoned.

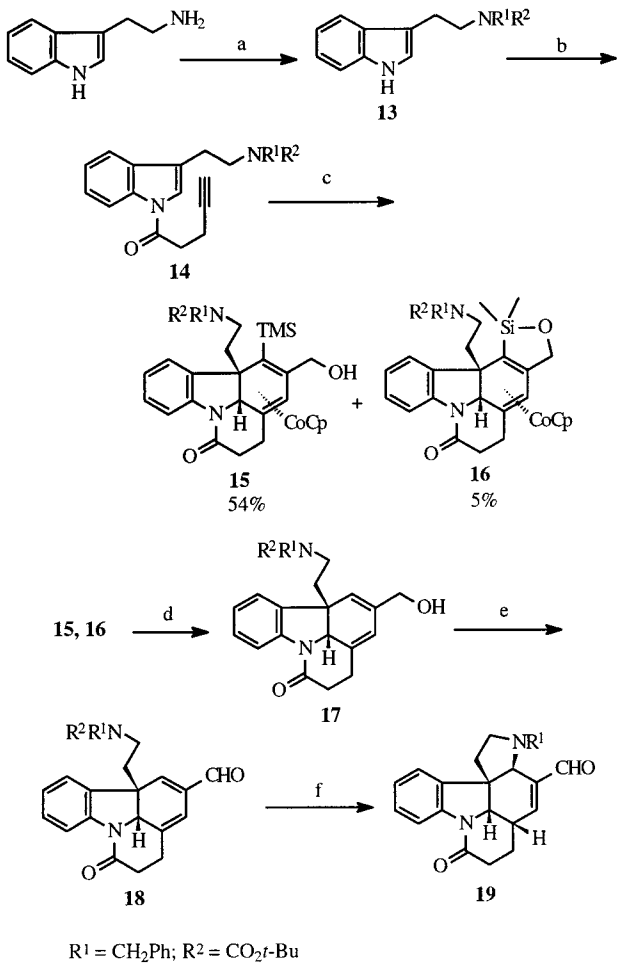
Unsuccessful AB → ABCD → ABCDE → ABCDEF Approaches to 1: Formation of Ring E from ABCD Intermediates

Given the impeded cyclization of the large constrained ring in **8**, an alternative route to **1** was developed via the successive formation of the E, F, and G rings of **1** from readily available *N*-(4-pentynoyl)indole cyclization products A (Scheme 2), such as those shown in Scheme 1. This strategy involved the synthesis of a highly functionalized ABCD ring system that would allow the closure of the E and F rings in a minimum number of steps. Thus, the following studies focused on the selection of an appropriate [2 + 2 + 2] cyclization partner for the alkyne-tethered indole system and the subsequent formation of the necessary C−N and C−C bonds. While ultimately unsuccessful, they provided some interesting insights into the virtually unknown chemistry of the dihydrocarbazole nucleus A (Scheme 2) accessed by our methodology.

E Ring via Intramolecular Conjugate Addition. The presence of a double bond at C15−C16 in the cycloaddition products suggested the use of a Michael addition for the formation of the C−N bond and the pyrrolidine ring. For this purpose, the unsaturated aldehyde **18** was synthesized as shown in Scheme 5. Cyclization precursor **14** was prepared from tryptamine in three steps and cyclized with 3-trimethylsilylpropyn-1-ol to yield **15** (34% from tryptamine), along with a small amount of internally cyclized **16** (5% from **14**). Structural and regiochemical assignments of the cyclohexadiene products were based on the ample precedent provided by similar systems[21a,25,35] and utilized the anisotropy of cobalt in ^{1}H NMR spectra. While spectrally similar to **15**, the identification of silyl ether **16** was based on mass spectrometry ($M^+ = 666$, indicating a loss of CH_4 with respect to **15**), the lack of a hydroxy group absorption in the IR spectrum, and the presence of two singlets at δ 0.38 (3H) and 0.24 (3H) ppm in the ^{1}H NMR spectrum.[36] Hydrolysis of the silicon−carbon bond in **15** and **16** with fluoride ion followed by demetalation with iron(III) afforded free ligand **17**, which was oxidized with MnO_2[37] to form the α,β-enal **18**. Finally, treatment of the aldehyde with TMSI gave the pentacycle **19** in 53% yield.[38]

Consistent with the formation of the pyrrolidine ring, the ^{13}C NMR-DEPT spectrum showed the disappearance of the methine carbon at δ 145.4 ppm and the quaternary carbon signal at δ 133.7 ppm assigned to C16 and C14, respectively, in **18** and two new methine signals upfield at δ 72.1 (C16) and 31.2 (C14) ppm. In the ^{1}H NMR spectrum, the signal assigned to the C16 methine at δ 6.26 (s, 1H) ppm in **18** was replaced by a signal at δ 3.38 (s, 1H) ppm. The ^{1}H NMR spectrum of **19** also displayed a doublet at δ 4.27 (1H) ppm that was assigned to the hydrogen at C8, exhibiting a coupling constant of 3.9 Hz. This value is consistent with the presence of the undesired cis relationship between the C8 and C13 methine hydrogens. In strychnine, the corresponding trans configured protons have a *J* value of 10.5 Hz.[39] Attempts to isomerize **19** with base (DBN, THF, 25 °C, 1 d) failed.

Scheme 5. Formation of E Ring via Intramolecular Conjugate Addition[a]

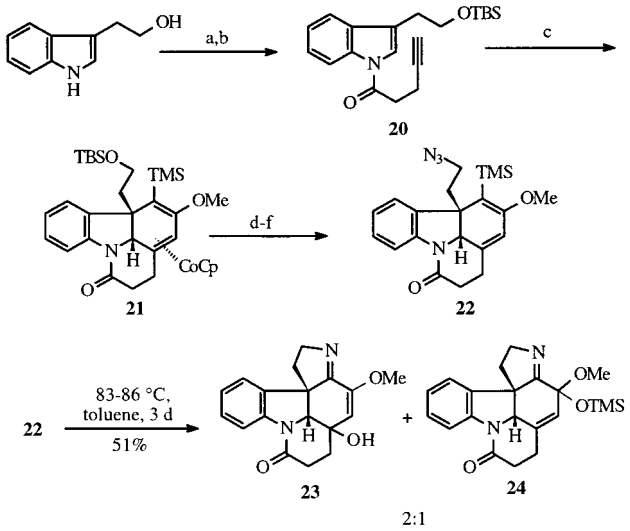


[a] Conditions: (a) i. PhCHO (1.1 equiv), MeOH, 25 °C, 1 h; ii. $NaBH_4$ (0.6 equiv), 25 °C, 10 min; iii. $(t\text{-}BuO_2C)_2O$ (1.4 equiv), CH_2Cl_2, 25 °C, 10 min, 84%; (b) i. KOH, glyme, 20 min; ii. 4-pentynoyl chloride, 0 °C, 5 min, 74%; (c) 3-trimethylsilylpropyn-1-ol (2 equiv), $CpCo(CO)_2$ (1.7 equiv), pyridine (0.5 equiv), *m*-xylene, reflux, 15 h; (d) i. Me_3BnNF (1.1 equiv), THF, reflux, 2−4 h; ii. $Fe(NO_3)_3 \cdot 9H_2O$ (3 equiv), THF, 0 °C, 5 min, 83%; (e) activated MnO_2 (13.2 mmol), CH_2Cl_2, 25 °C, 4 h, 88%; (f) i. TMSI (1.6 equiv), CH_2Cl_2, 25 °C, 20 min; ii. $NaHCO_3$, H_2O−MeOH, 25 °C, 0.5 h, 53%.

E Ring via an Intramolecular Dipolar Cycloaddition. Another attractive method for the formation of the C−N bond involved an intramolecular [2 + 3] cycloaddition of an azide moiety with an enol ether unit at C15−C16,[40] followed by acid-catalyzed expulsion of nitrogen to form the desired pyrrolidine ring.[41] The precursor for this transformation was readily available in six steps from indole-3-ethanol[42] (Scheme 6). Cyclization of the silyl ether **20** with alkyne **9** afforded the desired product **21** in 60% yield.[25a] Simple functional group manipulation gave the azide **22** in 70% yield from **21**. Dipolar cycloaddition studies were conducted at mild temperatures (80−90 °C) to avoid nitrene formation and at low concentration

(35) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539.
(36) For precedence, see: (a) Uemura, M.; Kobayashi, T.; Isobe, K.; Minami, T.; Hayashi, Y. *J. Org. Chem.* **1986**, *51*, 2859. (b) Hillard, R. L., III; Vollhardt, K. P. C. *Tetrahedron* **1980**, *36*, 2435.
(37) Fatiadi, A. J. *Synthesis* **1976**, 65.
(38) (a) Greene, T. W.; Wuts, P. G. M. *Protective Group in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999; p 521. (b) Olah, G. A.; Narang, S. C. *Tetrahedron* **1982**, *38*, 2225.
(39) Carter, J. C.; Luther, G. W.; Long, T. C. *J. Magn. Reson.* **1974**, *15*, 122.
(40) (a) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 351. (b) Padwa, A. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 2, p 277.
(41) Uhle, F. C. *J. Org. Chem.* **1967**, *32*, 1596.
(42) Nogrady, T.; Doyle, T. W. *Can. J. Chem.* **1964**, *43*, 485.

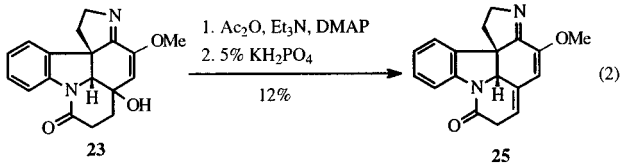
Scheme 6. Preparation and Dipolar Cycloaddition of Azide **22**[a]



[a] Conditions: (a) *t*-BuSiMe$_2$Cl (1.2 equiv), imidazole (2 equiv), DMF, 25 °C, 24−36 h; (b) i. KOH (1.2 equiv), glyme, 0 to 25 °C, 10 min; ii. 4-pentynoyl chloride (1.3 equiv), 0 °C, 20 min, 56% (2 steps); (c) **9** (2.5 equiv), $CpCo(CO)_2$ (1.8 equiv), *m*-xylene, reflux, 28 h, 60%; (d) Bu_4NF, THF, 25 °C, 1.25 h, 100%; (e) i. $MeSO_2Cl$ (2 equiv), Et_3N, CH_2Cl_2, 0 °C, 10 min; ii. NaN_3 (1.6 equiv), DMF, 70 °C, 8 h, 86%; (f) $CuCl_2 \cdot 2H_2O$ (5 equiv), Et_3N (2 equiv), 0 °C, 15 min, 80%.

(0.005 M) to suppress intermolecular reactions. Thermolysis in toluene gave, after 3 days, two products, **23** and **24**, in the ratio of 2:1 in 51% overall yield. Switching to a more polar solvent[43] (DMF, 80 °C, 7 d) gave a 5:1 ratio of the cyclized products in 53% overall yield.

The presence of a hydroxy group in **23** was indicated by a strong, broad absorption at 3300 cm^{-1} in the infrared spectrum and its location at C13 by a singlet for the C8 methine at δ 4.36 (1H) ppm in the ^{1}H NMR spectrum. The stereochemistry of the hydroxy group could not be determined unequivocally from the spectral data. The presence of the imine and enol ether functionalities was evident from ^{13}C NMR signals at δ 169.2 (C16), 154.6 (C15), and 108.8 (C14) ppm and a peak at δ 5.16 (s, 1H) ppm corresponding to the olefinic proton. Chemical support for this assignment was given by the acetylation of **23** and subsequent elimination to form **25** (eq 2). The presence of



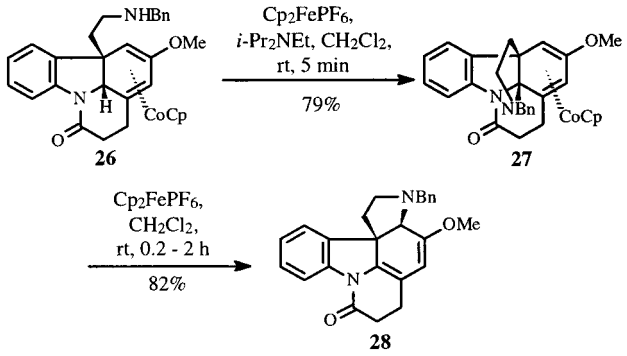
(2)

the imine and silylated acetal functionalities in **24** was suggested by quaternary carbon resonances at δ 169.87 (C16) and 92.76 (C15) ppm, as well as by ^{1}H NMR NOE experiments. Irradiation of the singlet at δ 0.17 (3H) ppm, corresponding to the trimethylsilyl group, led to an enhancement of the methoxy singlet at δ 3.04 (3H) ppm and the olefinic signal at 5.74 (s, 1H) ppm. Furthermore, the singlet resonance at δ 4.41 (1H) ppm for the C8 methine hydrogen indicated unsaturation at the adjacent C13.

Although the lack of an isolable 1,2,3-triazoline intermediate precluded the application of Uhle's acid-catalyzed decomposition to an amine, the isolation of the analogous imines displaying

(43) Kadaba, P. K. *Synthesis* **1973**, 71.

Scheme 7. Oxidative Cyclization and Rearrangement of **26**[21a]



the desired (albeit oxidized) pyrrolidine ring was gratifying.[44,45] However, the incorporation of oxygen into these products, despite efforts to exclude it, indicates that the cycloaddition intermediates (which may be either zwitterionic[46] or radical[47] in nature) are remarkably efficient scavengers of O_2.[48] Nevertheless, diene **25** represented a promising ABCDE intermediate and contained the desired C12−C13 double bond of isostrychnine (**2**). The required cis fusion of the pyrrolidine ring system was anticipated to be available by a selective reduction of the imine. However, we chose to abandon this approach given the poor yields of the dipolar cycloaddition and the difficulty of the piperidine ring formation employing the enol ether functionality encountered in studies of **28** and **30b** (vide infra).

E Ring via Oxidative Cyclization and Rearrangement and Attempts to Elaborate to F Ring. The most promising lead for a successful utilization of structures of type A (Scheme 2) was provided by the discovery that complex **26**, prepared as in Scheme 1, could be converted to the propellane **27** by oxidation with Cp_2FePF_6 and subsequently rearranged to the ABCDE framework of strychnine in **28** upon removal of the cyclopentadienyl cobalt unit under oxidative conditions in 65% overall yield (Scheme 7).[21a] Thus, with efficient access to the desired pentacyclic system in hand, the opportunity presented itself to utilize the functionalized D ring for the formation of the F ring and in the process restore the required cis juncture between the C and D rings. Attempts to hydrolyze the dienol ether system in **28**, however, were unsuccessful, resulting in either no reaction (THF/H_2O/HOAc (3:3:1), 25 °C, 5 d) or decomposition (CF_3CO_2H or HCl, Δ). Presumably, this difficulty is due to protonation of the tertiary nitrogen and the subsequent dipolar repulsion slowing the rate of hydrolysis. Attempts to obviate this problem by replacing the *N*-benzyl moiety with an electron-withdrawing substituent were thwarted by the resistance of **28** to catalytic hydrogenation (Pd−C, HOAc/MeOH) at 1 atm of H_2 and its decomposition at higher pressures (3 atm). An alternative strategy for the activation of **28** toward hydrolysis

(44) Logothetis, A. L. *J. Am. Chem. Soc.* **1965**, *87*, 749.

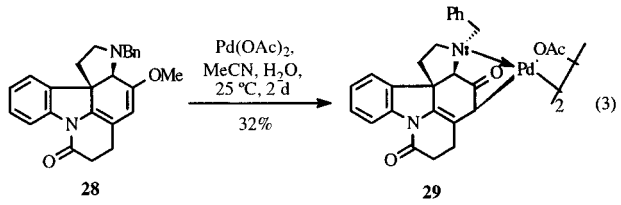
(45) For examples of the application of the imine products of a 1,3-dipolar cycloaddition of azides and olefins toward alkaloid synthesis, see: (a) Pearson, W. H.; Schkeryantz, J. M. *J. Org. Chem.* **1992**, *57*, 6783. (b) Bennet , R. B., III; Chooi, J.-R.; Montgomery, W. D.; Cha, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 2580. (c) Taber, D. F.; Deker, P. B.; Fales, H. M.; Jones, T. H.; Lloyd, H. A. *J. Org. Chem.* **1988**, *53*, 2968.

(46) (a) Smith, P. A. S.; Chou, S. P. *J. Org. Chem.* **1981**, *46*, 3970. (b) Scheiner, P. In *Selective Organic Transformations*; Thyagarajan, B. S., Ed.; Wiley: New York, 1970; p 327.

(47) (a) Pearson, W. H.; Bergmeier, S. C.; Degan, S.; Lin, K.-C.; Poon, Y.-F.; Schkeryantz, J. M.; Williams, J. P. *J. Org. Chem.* **1990**, *55*, 5719. (b) Broeckx, W.; Overbregh, N.; Samyn, C.; Smets, G.; L'abbé, G. *Tetrahedron* **1971**, *27*, 3527. (c) Reference 46b, p 347.

(48) Nelsen, S. F.; Teasley, M. F.; Kapp, D. L. *J. Am. Chem. Soc.* **1986**, *108*, 5503.

could involve the π-complexation of a metal cation to the electron-rich diene system. On the basis of the well-known Pd(II)-mediated addition of nucleophiles to alkenamines, it was anticipated that the enol ether function in **28** would add H_2O in the presence of Pd(II).[49] Interestingly, exposure of **28** to a slight excess of $Pd(OAc)_2$ led to the isolation of **29** in 32% yield (eq 3).



28 **29**

The ^{13}C NMR-DEPT spectrum of **29** indicated the presence of a ketone by displaying a quaternary carbon signal at δ 199.43 ppm, in addition to peaks at δ 182.22 and 165.54 ppm corresponding to the acetate and amide carbonyls, respectively. This observation also supported the structural assignment of **29** as a σ-palladium complex rather than as the π-oxoallyl or π-allyl derivative, as did the signal assigned to the methine carbon α to the palladium atom at δ 43.74 ppm, significantly upfield from typical palladium complexed π-allyl terminal carbons.[50] Additionally, a strong, high-energy absorbance at 1684 cm^{-1} in the IR spectrum, assigned to both the amide and ketone carbonyls,[51] discounted the association of the Pd center with the D ring carbonyl (an equally strong absorbance at 1570 cm^{-1} was assigned to the Pd-coordinated acetate ligand).

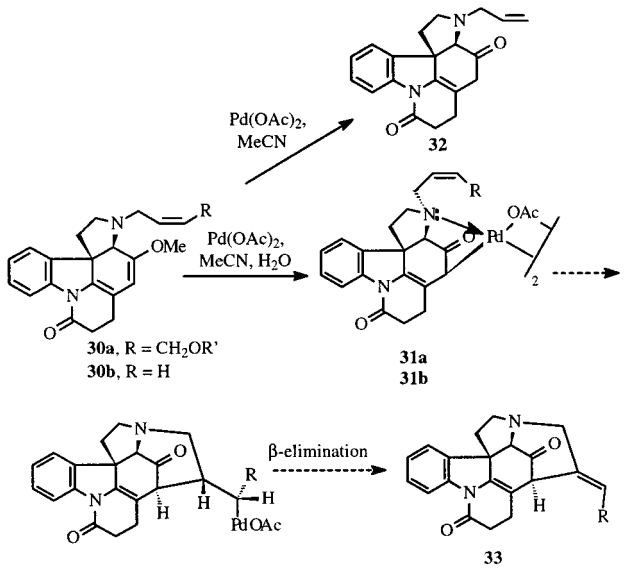
The isolation of **29** suggested the exploitation of the existing Pd−C linkage for carbon−carbon bond formation with an appropriate nitrogen side chain. In particular, the intramolecular syn insertion of the allylic double bond in the *trans*-butenyl substituent in **30a** and subsequent syn β-hydride elimination would give the desired *E*-alkene **33** (Scheme 8). This proposal was examined with alkene **30b**[21a] as a model. Upon exposure to $Pd(OAc)_2$ under the conditions used for **28**, only a low yield (ca. 25%) of impure complex **31b**, tentatively identified by the similarity of its spectral properties to **29**, was obtained, perhaps due to competing Wacker-type oxidation of the alkene function. Reaction of **30b** in the absence of water gave **32**, tentatively identified as the hydrolyzed enone based on ^1H NMR and on IR peaks at 1722 and 1691 cm^{-1} for the ketone and amide carbonyls, respectively. Thus, despite the successful rearrangement of **26** to form the E ring, difficulties in elaborating ring D in **28** led to the abandonment of this strategy.

The AB → ABCD → ABCDE → ABCDEF Approach to 1: Successful Strategy via an ABCD Trienamide

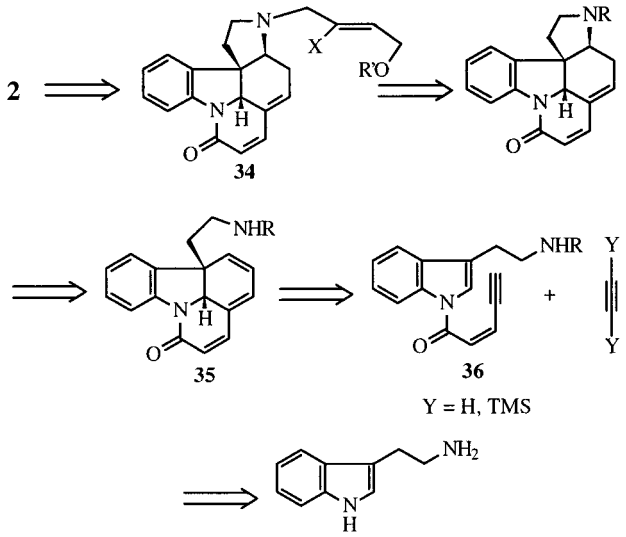
Up to this point, the attempts to form rings E and F involved functional group placement on the D ring to facilitate the necessary C−N and C−C bond formation reactions. However, as this work progressed, it became clear that the required chemistry was not only not forthcoming, but that it would be cumbersome even if successful. Instead, a more streamlined synthesis was sought that would eliminate the need for auxiliary substitution of the D ring. Scheme 9 illustrates such a strategy. In this approach, formation of the E and F rings would proceed via nucleophilic addition to an extended π-system activated by the amide carbonyl function. More specifically, the pyrrolidine ring E would be made by a formal intramolecular 1,8-Michael addition of precursor **35** and the piperidine ring via the conjugate addition of a *Z*-4-hydroxy-2-butenyl unit, properly functionalized at the 2-position, to C14 in **34**. The required **35** was anticipated to be readily available by [2 + 2 + 2] cycloaddition of an enynoylindole of the type **36** to bis(trimethylsilyl)acetylene (BTMSA), followed by desilylation, or to acetylene, a previously untried cocyclization partner for the indole and related systems.[25a]

First Synthesis of Enynoylindole 40. We envisioned a straightforward synthesis of the cyclization precursor **40** via an acylation of acetyltryptamine[52] (**37**) with *cis*-3-iodoacryloyl chloride,[53] followed by Pd-mediated coupling with trimethylsilylacetylene and desilylation. Surprisingly, conditions that had

Scheme 8. Attempted Pd-Mediated Conversion of Enol Ether **30** to Hexacycle **33**



Scheme 9. Synthetic Approach to **2** via a Double Conjugate Addition



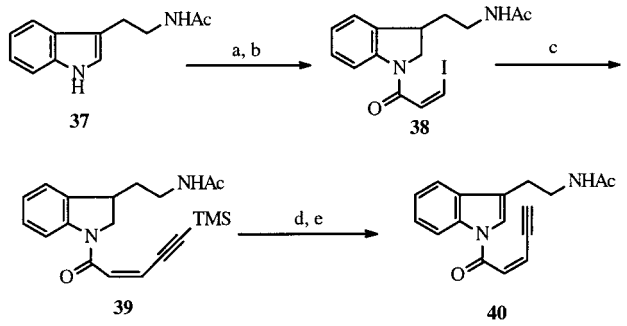
(49) (a) Tsuji, J. *Palladium Reagents and Catalysis*; Wiley: New York, 1995; pp 21−50. (b) Holton, R. A.; Kjonaas, R. A. *J. Am. Chem. Soc.* **1977**, *99*, 4177. (c) Alyea, E. C.; Dias, S. A.; Ferguson, G.; McAlees, A. J.; McCrindle, R.; Roberts, P. J. *J. Am. Chem. Soc.* **1977**, *99*, 4985. (d) McCrindle, R.; Ferguson, G.; Khan, M. A.; McAlees, A. J.; Ruhl, B. L. *J. Chem. Soc., Dalton Trans.* **1981**, 986.

(50) (a) Pregosin, P. S.; Salzmann, R. *Coord. Chem. Rev.* **1996**, *115*, 35. (b) Hunt, D. A.; Quante, J. M.; Tyson, R. L.; Dasher, L. W. *J. Org. Chem.* **1984**, *49*, 5262.

(51) (a) Ito, Y.; Aoyama, H.; Hirao, T.; Mochizuki, A.; Saegusa, T. *J. Am. Chem. Soc.* **1979**, *101*, 494. (b) Ito, Y.; Nakatsuka, M.; Kise, N.; Saegusa, T. *Tetrahedron Lett.* **1980**, *21*, 2873.

(52) Späth, E.; Lederer, E. *Chem. Ber.* **1930**, *63*, 120.

Scheme 10. First Synthesis of **40**[a]

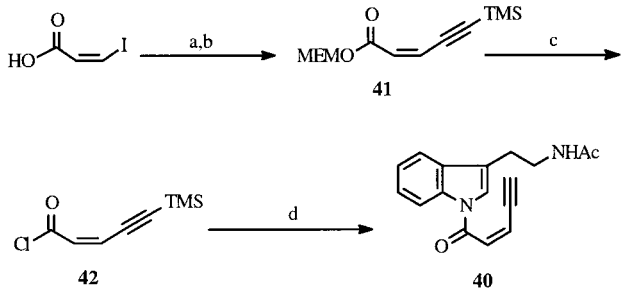


[a] Conditions: (a) H_2 (3.4 atm), 10% Pd−C, 1 N HCl−MeOH (1:1), room temperature, 2 d; (b) *cis*-3-iodoacryloyl chloride (1.5 equiv), 2,6-lutidine (1.4 equiv), CH_2Cl_2, 0 °C, 25 min, 71% (2 steps); (c) trimethylsilylacetylene (3.6 equiv), $Pd(PPh_3)_2Cl_2$ (0.04 equiv), CuI (4.5 equiv), Et_3N (2.1 equiv), C_6H_6, room temperature, 1 h, 78%; (d) MnO_2 (20 equiv), C_6H_6, 90 °C, 25 min, 63%; (e) $KF{\cdot}2H_2O$ (1.4 equiv), 18-crown-6 (0.03 equiv), THF, room temperature, 2 h, 85%.

previously worked well for the acylation of the indole nitrogen failed to yield any of the desired unsaturated amide product. Deprotonation of **37** with KOH in DME[32] followed by addition of the acid chloride returned only the starting indole. The same results were obtained upon deprotonation with BuLi[54] and weak amine bases[53b] (Et_3N, 2,4-lutidine). Attempted acylation employing Illi's phase transfer method was similarly disappointing.[55,56] Notably, the parent indole system also failed to acylate under these conditions, indicating that competing deprotonation of the amide hydrogen in **37** ($pK_a \cong 17$,[57] in comparison to $pK_a = 16.6$ for 3-methylindole[58]) was not detrimental.

To facilitate the formation of the amide, the nucleophilicity of the heterocyclic nitrogen center was increased by the reduction of the aromatic indole system to indoline (Scheme 10). Thus, catalytic hydrogenation of the indole double bond[59] followed by acylation with *cis*-3-iodoacryloyl chloride in the presence of 2,6-lutidine gave the amide **38**. Palladium-mediated coupling[33] with trimethylsilylacetylene afforded the enyne system **39** in 78% yield for the three steps. Rearomatization of the indoline by oxidation with DDQ[60] resulted in poor yields (31%) due to the instability of **39** to the reaction conditions. Dehydrogenation with Wilkinson's catalysts[61] also destroyed the rather sensitive indoline. However, oxidation with activated MnO_2[37,62] in refluxing benzene gave the desired oxidized indole system in a moderate 63% yield.[63] Finally, desilylation with KF[64] afforded the enynoylindole **40** in 36% yield for the entire sequence.

Scheme 11. Second Synthesis of **40**[a]



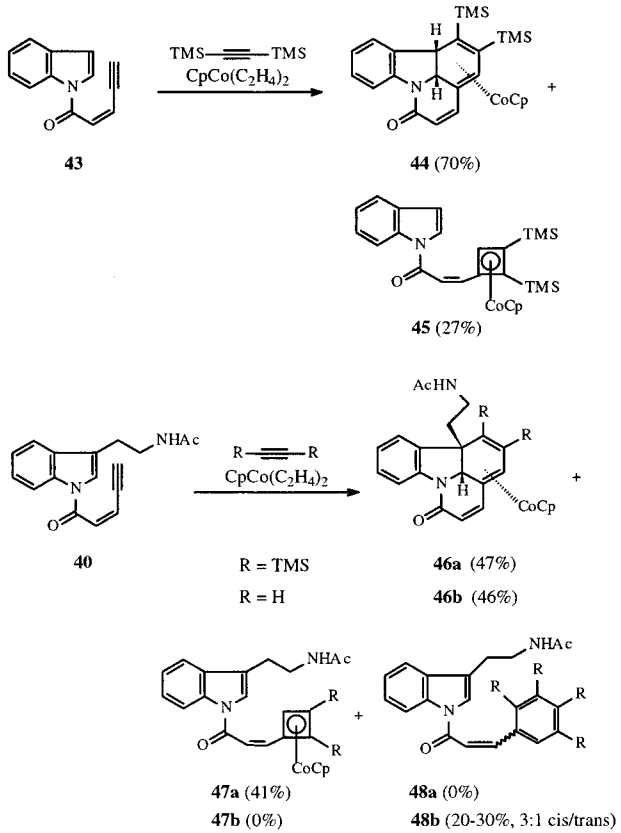
[a] Conditions: (a) MEMCl (14 equiv), Na_2CO_3 (12 equiv), DMF, room temperature, 50 min, 86%; (b) trimethylsilylacetylene (2 equiv), $Pd(PPh_3)_2Cl_2$ (0.05 equiv), CuI (0.1 equiv), Et_3N, room temperature, 1 h, 98%; (c) i. 3 N HCl, THF, room temperature, 3 d; ii. $(COCl)_2$, room temperature, 14 h, 83%; (d) **37** (0.76 equiv), NaOH (7.7 equiv), Bu_4NCl (0.9 equiv), H_2O (2.5 equiv), CH_2Cl_2, 0 °C, 50 min, 86% based on **37**.

Second Synthesis of 40. The five-step synthesis described above proved to be too cumbersome for the production of sufficient quantities of the [2 + 2 + 2] cycloaddition precursor **40** for subsequent studies. For this reason, a more convergent route to the enynoylindole was developed (Scheme 11).[20] This path involved the construction of the cis enyne before acylation, by the coupling of *cis*-3-iodoacrylic acid 2-methoxyethoxymethyl ester with trimethylsilylacetylene to afford **41**. Conversion to the acid chloride **42** was achieved by ester hydrolysis[65] and reaction with oxalyl chloride. Gratifyingly, the indole nitrogen of **37** could not only be acylated with **42**, but the product was also simultaneously desilylated by modification of the original phase-transfer conditions.[55] Rapid addition of the acid chloride to a CH_2Cl_2 solution of acetyltryptamine in the presence of powdered NaOH, Bu_4NCl, and H_2O gave good yields (86%) of the enynoylindole **40**.[66,67] This five-step sequence was readily scaled up to afford multigram quantities of **40**.

[2 + 2 + 2] Cycloaddition of 40 with BTMSA and Acetylene. With enyoylindole **40** in hand, the cocyclization of **40** with acetylene and BTMSA, the latter with potentially cleavable carbon−silicon bonds, was examined (Scheme 12). BTMSA is a commonly employed acetylene surrogate in the cobalt-mediated [2 + 2 + 2] cycloaddition reaction due to its ease of use and resistance to autocyclization. Indeed, initial studies proved promising. Utilizing the reactivity of $CpCo(C_2H_4)_2$ at lower temperatures to minimize cyclobutadiene formation, reaction of unsubstituted enynoylindole **43** gave a favorable yield of **44** (70%) versus **45** (27%). Encouraged by this result, the cocyclization of **40** with BTMSA was examined. However, this reaction gave significantly more of the undesired cyclobutadiene complex **47a** (41%) at the expense of **46a** (47%). This result was not too surprising, given that the effect of 3-substitution on the indole nucleus has previously been shown to be a significant hindrance to the successful cyclization of *N*-(4-penynoyl)indoles with BTMSA.[25a] Switching to acetylene was thought to help in this regard and, moreover, would eliminate the need to remove silyl substituents in later steps.[68]

(53) (a) Moss, R. A.; Wilk, B.; Krogh-Jespersen, K.; Westbrook, J. D. *J. Am. Chem. Soc.* **1989**, *111*, 6729. (b) Wilson, R. M.; Commons, T. J. *J. Org. Chem.* **1975**, *50*, 4467.
(54) De Silva, S. O.; Snieckus, V. *Can. J. Chem.* **1978**, *56*, 1621.
(55) Illi, V. O. *Synthesis* **1979**, 387.
(56) For another study of indole acylation, see: Ottoni, O.; Cruz, R.; Alves, R. *Tetrahedron* **1998**, *54*, 13915.
(57) Homer, R. B.; Johnson, C. D. In *The Chemistry of Amides*; Zabicky, J., Ed., Wiley: New York, 1970; pp 188−197.
(58) Remers, W. A. In *Indoles*; Houlihan, W. J., Ed.; Wiley: New York, 1972; Part One, p 14.
(59) Daly, J. W.; Mauger, A. B.; Yonemitsu, O.; Antonov, V. K.; Takase, K.; Witkop, B. *Biochemistry* **1967**, *6*, 648.
(60) (a) Feng, H.; Foxman, B. M.; Snider, B. B. *J. Am. Chem. Soc.* **1998**, *120*, 6417. (b) Ono, S.; Yamafuji, T.; Chaki, H.; Morita, H.; Todo, Y.; Okada, N.; Maekawa, M.; Kitamura, K.; Tai, M.; Marita, H. *Chem. Pharm. Bull.* **1995**, *43*, 1492. (c) Fu, P. P.; Harvey, R. G. *Chem. Rev.* **1978**, *78*, 317.
(61) Nishiguchi, T.; Tachi, K.; Fukuzumi, K. *J. Org. Chem.* **1975**, *40*, 237.
(62) Fatiadi, A. J. *Synthesis* **1976**, 133.
(63) (a) Bonnaud, B.; Bigg, D. C. H. *Synthesis* **1994**, 465. (b) Stamos, I. K. *Tetrahedron* **1981**, *37*, 1813. (b) Kametani, T.; Ohsawa, T.; Ihara, M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 290.
(64) Carpino, L. A.; Sau, A. C. *J. Chem. Soc., Chem. Commun.* **1979**, 514.
(65) Abarbri, M.; Parrain, J.-L.; Cintrat, J.-C.; Duchêne, A. *Synthesis* **1996**, 82.
(66) The choice of the phase-transfer catalyst turned out to be critical to the success of the reaction. Use of Bu_4NHSO_4, as was originally described in Illi's paper (ref 55), gave no trace of **40**, while most other tetraalkylammonium salts examined generated at least some of the desired product.
(67) Oldroyd, D. L.; Weedon, A. C. *J. Org. Chem.* **1994**, *59*, 1333.

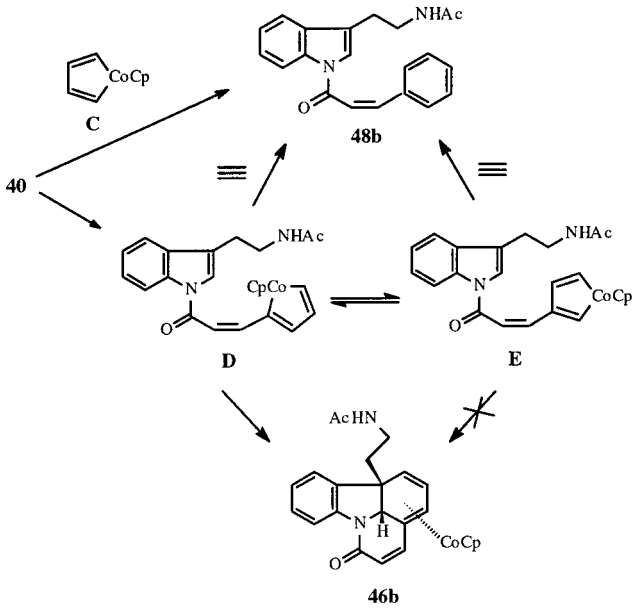
Scheme 12. [2 + 2 + 2] Cycloaddition of *N*-(Pent-2-en-4-ynoyl)indoles **40** and **43**



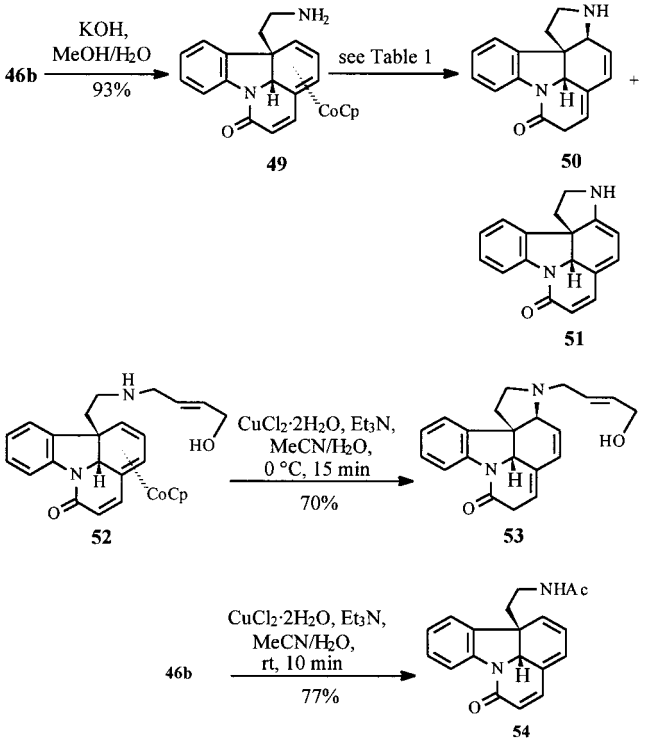
Initial experiments with **40** and acetylene were performed on a submillimolar scale. When $CpCo(C_2H_4)_2$ (3.5 equiv) was added to a solution of **40** (0.12 mmol) in THF that had been saturated with acetylene gas,[69] the desired dihydrocarbazole complex **46b** was formed in 43% yield. Attempts to scale-up the procedure to 0.5 mmol of **40** or more led to a significant decrease in yield (17−24%). The main product of the reaction was **48b**, isolated in 50−60% yield as a mixture of cis and trans isomers. The loss of the cis stereochemistry seems to be associated with catalysis by the cobalt center, the scope and nature of which is currently under investigation.[70]

Cinnamic amide **48b** may be formed by two pathways, the reaction of **40** with C, formed from two molecules of acetylene, or of either (or both) of the metallacyclopentadiene intermediates D or E with acetylene (Scheme 13).[35,71] Consideration of Scheme 13 suggested that yields of **46b** might be improved by reducing the steady state acetylene concentration in the reaction mixture. This modification would retard the formation of C and the trapping of (the presumably equilibriating)[35] D and E by acetylene. Indeed, by moderating the rate of acetylene addition and concomitantly purging the mixture with a stream of nitrogen or argon, performing the cyclization under dilute conditions (0.05 M as the initial concentration of **40**), and maintaining a temperature of 0 °C, the reaction was optimized at a 1 g (3.5 mmol) scale to afford **46b** in 46% with a 20−30% yield of

Scheme 13. Pathways for Formation of **46b** and **48b** from **40**



Scheme 14. Formation of E Ring during Demetalation of Complexed Cyclohexadienes



48b (3:1, cis/trans). Other changes such as solvent (benzene, EtOAc, Et_2O, CH_2Cl_2), rate or order of addition of the nongaseous reagents, use of alternative CpCo sources [$CpCo(CO)_2$ or $Cp^*Co(C_2H_4)_2$[72]], or additives (PPh_3)[73] were inconsequential or led to reductions in yield.

Demetalation of 46b and Formation of E Ring. Construction of the fifth ring of **1** is shown in Scheme 14. Notably, the acetamide function of **46b** could be hydrolyzed under the rather harsh conditions required [KOH (165 equiv), MeOH/H_2O (1:

(68) Indeed, attempted removal of both of the silicon groups in **46a** either failed [$Bn(CH_3)_3NF$ and CsF] or led to decomposition (CF_3CO_2H).

(69) Fogg, P. G. T.; Gerrard, W. *Solubility of Gases in Liquids*; Wiley: New York, 1991; pp 146−153.

(70) Stirring **48b**-*cis* with substoichiometric amounts of $CpCo(C_2H_4)_2$ at room temperature led to complete conversion to **48b**-*trans* within 2 h.

(71) (a) Hardesty, J. H.; Koerner, J. B.; Albright, T. A.; Lee, G.-Y. *J. Am. Chem. Soc.* **1999**, *121*, 6055. (b) Diercks, R.; Eaton, B. E.; Gürtzgen, S.; Jalisatgi, S.; Matzger, A. J.; Radde, R. H.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1998**, *120*, 8247.

(72) Beevor, R. G.; Frith, S. A.; Spencer, J. L. *J. Organomet. Chem.* **1981**, *221*, C25.

(73) Stara, I. G.; Stary, I.; Kollarovic, A.; Teply, F.; Saman, D.; Tichy, M. *J. Org. Chem.* **1998**, *63*, 4046.

Table 1. Oxidative Demetalation of **49**

entry	oxidizing agent[b]	solvent	*T* (°C) (*t* [min])	yield of products, %[a] **50**	**51**
1	$CuCl_2 \cdot 2H_2O/Et_3N$	$MeCN/H_2O$	0 (10)	51	
2	$CuCl_2 \cdot 2H_2O/Et_3N$	$MeCN/H_2O$	25 (10)	58	
3	$CuCl_2 \cdot 2H_2O$	$MeCN/H_2O$	25 (60)	48	
4	$FeCl_3 \cdot 6H_2O$[c]	MeCN	0 (20)	66	
5	$Fe(NO)_3 \cdot 9H_2O$	$MeCN/THF/H_2O$	0 (15)	77	
6	Cp_2FePF_6[d]	CH_2Cl_2	25 (120)		37
7	$(NH_4)_2Ce(NO_3)_6$	MeCN/THF	−78 (15)	trace	trace

[a] Isolated yields. [b] Unless otherwise noted, a 3- to 5-fold excess of the oxidizing reagent was used. [c] 2 equiv used. [d] 1.1 equiv used.

1), reflux, 6 h] without significant decomposition to give the amine **49** in 93% yield. It is possible that the electron-donating and bulky CpCo moiety stabilizes the amide bond in ring C, preventing hydrolysis to the indoline carboxylic acid.[12] Gratifyingly, the complexed diene could be readily demetalated oxidatively to form the E ring of strychnine. A number of reagents were examined for this transformation (Table 1). Copper(II)[21a,24c,25a,35] and two iron(III) systems gave the desired secondary amine **50** as the only isolable product. The best yields (77%) were obtained with $Fe(NO)_3 \cdot 9H_2O$[25a] (entry 5). Notably, **50** was isolated as the C12−C15 diene, as opposed to the more stable diene system in conjugation with the carbonyl (i.e., **63**, described below). The ^{1}H NMR spectrum showed olefinic signals at δ 5.75 (d, J = 10.0 Hz, 1H), 5.95 (m, 1H), and 6.33 (dd, J = 10.0, 2.5 Hz, 1H) ppm, assigned to the C14, C12, and C15 methine hydrogens, respectively. Use of Cp_2FePF_6 led to low yields of enamine **51**, most likely the result of overoxidation of **50**.[21a] The ^{1}H NMR spectrum of **51** showed olefinic signals at δ 7.20 (d, J = 9.2 Hz, 1H), 6.38 (d, J = 9.2 Hz, 1H), 6.24 (dd, J = 9.7, 2.3 Hz, 1H), and 5.46 (dd, J = 9.7, 2.0 Hz) ppm. Reaction with ceric ammonium nitrate gave a complex mixture of products in which **50** and **51** could be identified in only trace amounts.

Formation of the E ring also proved sensitive to the nature of the substituent on the exocyclic nitrogen. Thus, secondary amine **52**[74] gave good yields (66%) of the pentacyclic system **53** upon reaction with $CuCl_2 \cdot 2H_2O$, while the acetylated **46b** underwent only demetalation to form **54** in 77% yield under similar conditions. Although a formal 1,8-conjugate addition, the E ring closure occurred under conditions similar to those used for the rearrangement of **26** to **28** discussed above (Scheme 7) and may proceed through a radical cation cobalt species.[21a]

Secondary amine **50** represented a useful synthetic intermediate for the construction of the F ring by allowing the attachment of whatever functionalized side chain proved necessary for the critical C14−C21 bond forming reaction. Pursuing the conjugate addition approach described in Scheme 9, **50** was alkylated with (*Z*)-1-bromo-4-*tert*-butyl(dimethyl)siloxy-2-iodobut-2-ene (**55**),[17] which contained not only a readily activated sp^2 carbon−iodine center amenable to a variety of carbon−carbon bond forming reactions (vide infra), but also the desired allylic ether stereochemistry present in **1**.[75] Thus, amine **50** was alkylated with **55** in the presence of Li_2CO_3 to form **57** in good yields (74%) and isomerized to the more stable **56** with an alkoxide base (Scheme 15). In an effort to form **56** in a single step, amine **50** was treated with **55** under a variety of conditions intended to effect both

(74) From the alkylation of **49** with *cis*-4-*tert*-butyl(dimethyl)siloxy-1-bromo-2-butene.

(75) Indeed, this stereochemical "problem" of strychnine synthesis has been solved by essentially the same approach by Stork (refs 11a and 18), Rawal (ref 17), and Bonjosch (ref 15).

Scheme 15. Synthesis of **56** and **59**

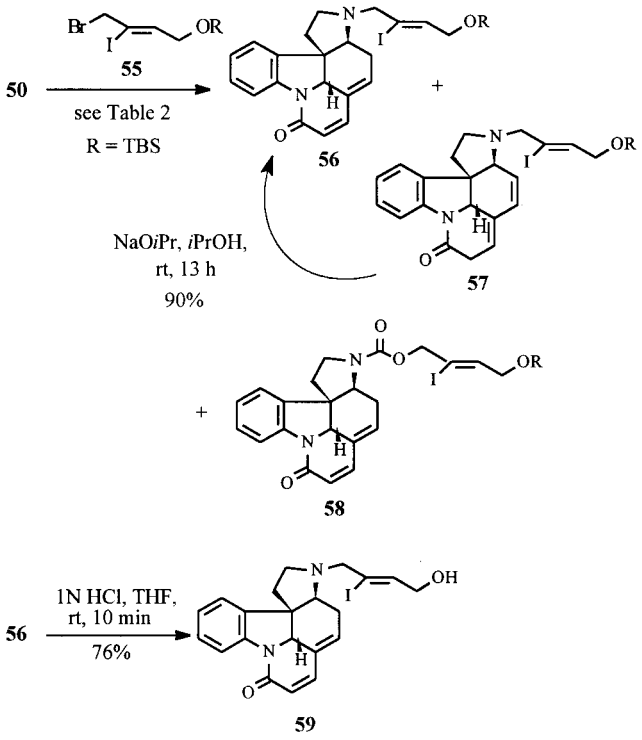


Table 2. One-Pot Alkylation and Isomerization of **50**[a]

entry	base	solvent	yield of products, %[b] **56**	**57**	**58**
1	K_2CO_3	acetone/DMF (5:1)[c]		50	
2	K_2CO_3	DMF	5		22
3	K_2CO_3	DMSO	3	23	trace
4	K_2CO_3	HMPA	23	23	18
5	K_2CO_3[d]	HMPA		64	8
6	Na_2CO_3	DMF		61	
7	Li_2CO_3	DMF		74	
8	K_3PO_4[d]	DMF[e]		47	
9	DBU[d]	DMF	12[f]		

[a] Unless otherwise indicated, reactions were run with 5 equiv of base and 1.1 equiv of **55** at 45 °C for 24 h. [b] Isolated yields. [c] See ref 17. [d] 2.5 equiv of base used. [e] Reaction run at room temperature. [f] A 3:7 mixture of starting amine **50** and its isomer **63** was isolated in 80% yield.

the alkylation and the isomerization of the diene system into conjugation with the amide carbonyl (Table 2). A number of carbonate, phosphate, as well as a hindered amine bases (DBU) were examined in various polar−aprotic solvents. These reactions either failed to lead to double bond isomerization or were complicated by formation of the carbamate **58** (in the presence of strong carbonate bases, entries 2−5)[76] or sluggish alkylation in the case of DBU (entry 9). For the purpose of confirming the structure and relative stereochemistry of **56** and related compounds, the allylic ether was deprotected with aqueous HCl in THF to form the highly crystalline alcohol **59** whose X-ray crystal structure was determined (Figure 4). The results confirmed the overall connectivity and stereochemistry.

Attempted Closure of F Ring via Conjugate Addition. The first strategy for closing the F ring featured an iodine−metal exchange and 1,6-conjugate addition to C14. Initial studies with alkyllithium reagents were disappointing. Addition of BuLi (1 equiv) to a THF solution of **56** at −78 °C followed by LiCu(thienyl)CN[77] gave a mixture from which only starting material

(76) Gómez-Parra, V.; Sánchez, F.; Torres, T. *Synthesis* **1985**, 282.

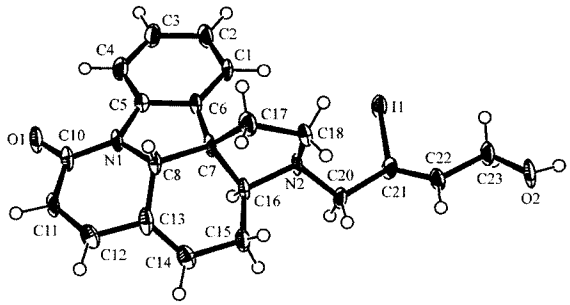
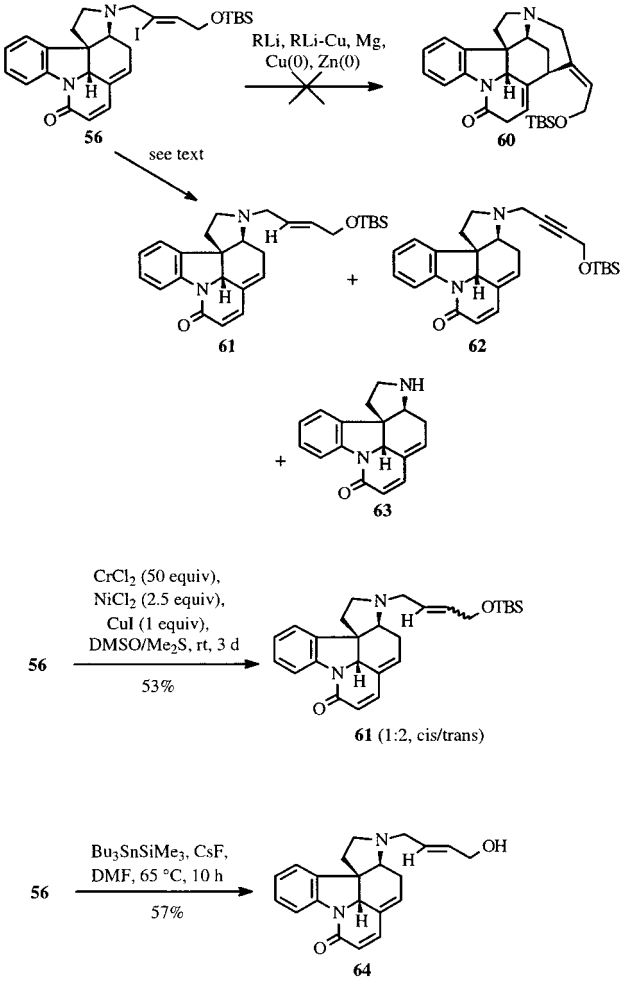


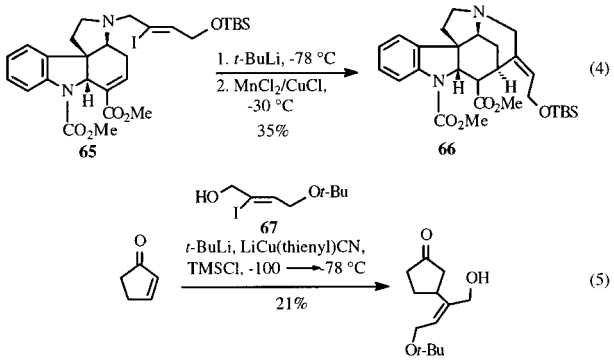
Figure 4. ORTEP diagram of **59**.

Scheme 16. Attempted Formation of F Ring by Anionic Conjugate Addition



(50%) could be isolated. Greater amounts of lithium reagent (2 equiv) led to complex mixtures containing no identifiable products. Reaction of BuLi (1.8 equiv) alone[78] at −100 °C gave, after 1 h, a mixture from which only deiodinated alkene **61** (19%) and alkyne **62** (6%)[79] could be isolated (Scheme 16). Analysis of the crude reaction mixture by GC/MS indicated the presence of a trace of the secondary amine **63**. This experiment indicated that the starting material, under the conditions of lithium−halogen exchange, was susceptible to a number of side reactions, including hydrogen iodide elimination, loss of the butenyl side chain, and deprotonation at C15.[80] Use of the more hindered base *t*-BuLi gave complex mixtures when reacted with **56** alone at −78 °C, or returned starting material combined with **61** on subsequent exposure to LiCu(thienyl)CN[81] or $MnCl_2$/CuCl.[82] Addition of TMSCl to activate the enone system also failed.

Other researchers have encountered similar difficulties in their attempts to construct the C14−C21 bond of **1** via a carbanion-mediated conjugate addition reaction. Stork and co-workers utilized a copper intermediate formed by a *t*-BuLi mediated iodine−lithium exchange, followed by the addition of $MnCl_2$/CuCl to convert diester **65** to the ABDEF intermediate **66** (eq 4).[11a,18] However, this reaction proceeded in poor yields (35%) and was difficult to reproduce.[83] Overman and co-workers were unable to obtain acceptable yields of the conjugate addition of allylic alcohol **67** to cyclopentenone on route to an early intermediate in their synthesis of **1**, and they eventually abandoned this approach (eq 5).[13] These workers attribute this difficulty to the destruction of the electrophile via the formation of allene byproducts,[81] a rationale that may also apply to our observation of amine **63**.



Other attempts to impart nucleophilicity to C21 of **56** proved similarly fruitless. Thus, the vinyl iodide could not be activated with magnesium to form the Grignard reagent[84] for subsequent transmetalation with copper.[85] Reactions either returned starting material (Mg, MeI, Et_2O, 40 °C, 4 d) or led to a complex mixture of products (Mg, TMSCl, 1,2-dibromoethane, THF, 65 °C, 1 d). Attempts at iodide−magnesium exchange with *i*-Pr_2Mg,[86] both with and without added Cu(I), led to extensive decomposition of the starting material. Activated copper[87] and zinc systems were also examined.[88] Addition of a THF solution of **56** and TMSCl to an activated Cu(0) mixture (generated by reduction of the CuCN·2LiBr complex at −100 °C with the naphthalene

(77) Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945.

(78) (a) Cooke, M. P. *J. Org. Chem.* **1993**, *58*, 2910. (b) Cooke, M. P. *J. Org. Chem.* **1992**, *57*, 1495.

(79) (a) Seebach, D.; Maestro, M. A.; Sefkow, M.; Adam, G.; Hintermann, S.; Neidlein, A. *Liebigs Ann. Chem.* **1994**, *7*, 701. (b) Katzenellenbogen, J. A.; Corey, E. J. *J. Org. Chem.* **1972**, *37*, 1441.

(80) Direct deprotonation at C15 may be responsible for the recovery of **56**. Alkene **61** may result from intramolecular proton transfer to the desired intermediate vinyl metal from C15.

(81) Angle, S. R.; Fevig, J. M.; Knight, S. D.; Marquis, R. W., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 3966.

(82) Alami, M.; Marquais, S.; Cahiez, G. *Org. Synth.* **1995**, *72*, 135.

(83) Stork, G., personal communication, 1999.

(84) (a) Piers, E.; Friesen. R. W. *Can. J. Chem.* **1992**, *70*, 1204. (b) Touet, J.; Baudouin, S.; Brown, E. *Tetrahedron: Asymmetry* **1992**, *3*, 587. (c) Hackett, M.; Whitesides, G. M. *J. Am. Chem. Soc.* **1988**, *110*, 1449.

(85) Posner, G. H. *Org. React.* **1972**, *19*, 1.

(86) Rottländer, M.; Boymond, L.; Cahiez, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 1080.

(87) (a) Rieke, R. D.; Klein, W. R.; Wu, T.-C. *J. Org. Chem.* **1993**, *58*, 2492. (b) Rieke, R. D.; Stack, D. E.; Dawson, B. T.; Wu, T.-C. *J. Org. Chem.* **1993**, *58*, 2483. (c) Ebert, G. W.; Rieke, R. D. *J. Org. Chem.* **1988**, *53*, 4482.

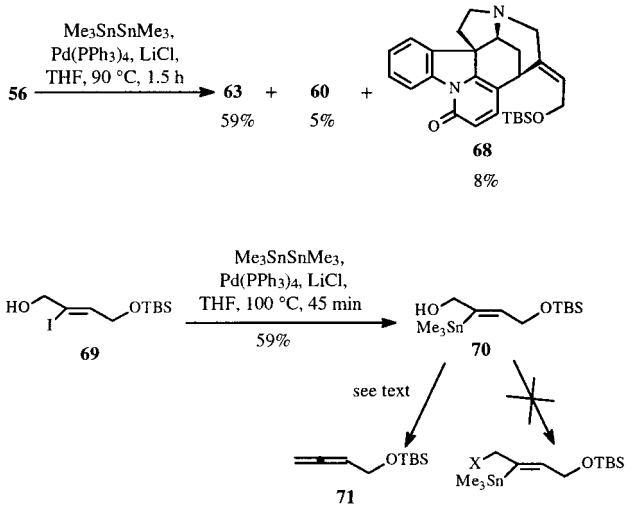
(88) (a) Hanson, M. V.; Rieke, R. D. *J. Am. Chem. Soc.* **1995**, *117*, 10775. (b) Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445. (c) Rieke, R. D. *Acc. Chem. Res.* **1977**, *10*, 301. (d) For a comprehensive review of organozinc reagents in organic synthesis, see: Knochel, P.; Perea, J. J. A.; Jones, P. *Tetrahedron* **1998**, *54*, 8275.

anion) resulted in no identifiable products. Similar results were obtained when **56** was added to a slurry of activated Zn(0) (prepared by reduction of $ZnCl_2$ in THF followed by, after overnight stirring, the addition of CuCN·2LiBr, TMSCl, and BF_3·OEt_2). Electron transfer from these active metal species or from residual naphthalene anion to the conjugated amide system may be responsible for the instability of the starting material under these conditions.

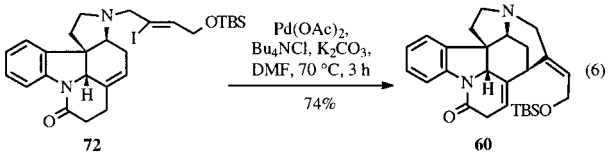
Because of these failures, a milder method for the activation of the pertinent carbon center was sought. Organochromium reagents have demonstrated excellent tolerance of functionality in the course of 1,2-additions to carbonyls.[89] Substituted vinyl halides have also been shown to insert Cr(II) readily.[90] Stirring **56** with $CrCl_2$ (3.5 equiv) doped with 5% $NiCl_2$[91] for 2 days in DMF returned the starting iodide (36%) and the dehalogenated alkene **61** (12%). Addition of CuI to the reaction mixture failed to lead to transmetalation of the intermediate chromium reagent to a more reactive organocuprate and gave, after 3 days, a 1:1 mixture of **61** and unreacted starting material (80% recovery). Reaction in DMSO/Me_2S gave partially isomerized alkene **61** in 53% yield (1:2, cis/trans)[92] (Scheme 16). Further attempts in pure DMSO, with a large excess of $CuCl_2$/$NiCl_2$,[93] the addition of certain additives (TMSCl), or reaction at elevated temperature (100 °C) failed.

Other mild approaches to potential carbanion formation involved transient organotin reagents. Recourse to trimethyl(tributylstannyl)silane in the presence of cesium fluoride[94] led to deiodinated, desilylated alkene **64** (57%) after 10 h in DMF at 65 °C (Scheme 16). Reaction in THF gave the deiodinated alkene **61** (55%), and addition of Lewis acids (TMSCl, BF_3·OEt_2), intended to activate the π-system, returned only starting material. Therefore, attempts were made at the assembly of an isolable alkenyltin reagent. Vinylstannanes are readily transmetalated by organocuprates[95] or Cu(I) salts (CuCl, CuCN).[96] Surprisingly, the attempted formation of the corresponding stannane by treatment of **56** with $Me_3SnSnMe_3$ and $Pd(PPh_3)_4$ in THF[13,97] in a sealed flask heated to 90 °C resulted in a mixture dominated by amine **63** (59%), but which also contained hexacyclic pyridone **68** as well as silylated isostrychnine (**60**)[17] in 8% and 5% isolated yields, respectively (Scheme 17). In contrast to amine **50**, (Scheme 14), **63** showed olefinic signals in the ^{1}H NMR spectrum at δ 6.90 (d, J = 9.7 Hz, 1H), 6.03 (d, J = 6.7 Hz, 1H), and 5.97 (d, J = 9.7 Hz, 1H) ppm, corresponding to the C12, C14, and C11 methine protons, respectively. Hexacyclic **68** displayed signals similar to **60** in the aliphatic region and peaks at δ 6.46 (d, J = 9.2 Hz, 1H) and 7.26 (d, J = 9.2 Hz, 1H) ppm, corresponding to C12 and C11 of the aromatic pyridone ring. Apparently, **60** and **68** result from the Pd-mediated addition of C21 to the C12−C13 double bond and either the intermolecular reduction of the Pd−C carbon bond or β-elimination of the C8 hydrogen (vide infra). Attempted installation of the trimethyltin moiety on the butenyl side chain prior to alkylation of **50** was successful with iodo alcohol **69** (an intermediate in the synthesis of **55**)[17] providing the vinyl tin **70** (Scheme 17). However, any effort to convert the hydroxy substituent into a leaving group, including bromination and sulfonate ester formation, resulted in rapid β-elimination to form allene **71**,[98] even at −78 °C.[99]

Scheme 17. Attempted Formation of a Stannylated Side Chain



Palladium- and Nickel-Mediated Formation of the F Ring. In Rawal and Iwasa's total synthesis of (±)-**1**, the critical C14−C21 bond is generated via an intramolecular Heck reaction of **72** to provide **60** (eq 6),[17] and it was therefore of interest to investigate the behavior of **56** under the same or related conditions (Scheme 18, Table 3). Notably, in the case of **72**,



(6)

while Pd-mediated coupling could terminate in the β-elimination of either the C8 or C12 hydrogens, only the latter is observed.[100] Pentacycle **61** has only the C8 hydrogen available, and indeed, upon exposure to Rawal's conditions, only aromatic pyridone **68** is isolated (Scheme 18, Table 3, entry 8). In an effort to suppress β-elimination, **56** was subjected to Heck cyclization conditions in the presence of a hydride source. Reactions of this type have been used to trap the intermediate palladium σ-complex before elimination or when no elimination pathway is readily available. Stirring **56** with catalytic $Pd(OAc)_2$/PPh_3 in the presence of sodium formate (1.7 equiv) and Et_4NCl in

(89) For a comprehensive review of carbon−carbon bond formation with organochromium reagents, see: (a) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991. (b) Wessjohann, L. A.; Scheid, G. *Synthesis* **1999**, 1.

(90) Kress, M. H.; Ruel, R.; Miller, W. H.; Kishi, Y. *Tetrahedron Lett.* **1993**, *34*, 6003.

(91) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644.

(92) Stereochemical equilibration of trisubstituted iodoolefins in nickel-catalyzed reactions has been observed. See: (a) Zembayashi, M.; Tamao, K.; Kumada, M. *Tetrahedron Lett.* **1975**, *16*, 1719. (b) Reference 91.

(93) Roe, M. B.; Whittaker, M.; Proctor, G. *Tetrahedron Lett.* **1995**, *36*, 8103.

(94) (a) Mori, M.; Isono, N.; Wakamatsu, H. *Synlett* **1999**, 269. (b) Imai, A. E.; Sato, Y.; Nishida, M.; Mori, M. *J. Am. Chem. Soc.* **1999**, *121*, 1217.

(95) Behling, J. R.; Babiak, K. A.; Ng, J. S.; Campbell, A. L.; Moretti, R.; Koerner, M.; Lipshutz, B. H. *J. Am. Chem. Soc.* **1988**, *110*, 2641.

(96) (a) Piers, E.; McEachern, E. J.; Burns, P. A. *Tetrahedron* **2000**, *56*, 2753. (b) Piers, E.; Skupinska, K. A.; Wallace, D. J. *Synlett* **1999**, 1867. (c) Piers, E.; McEachern, E. J.; Burns, P. A. *J. Org. Chem.* **1995**, *60*, 2322.

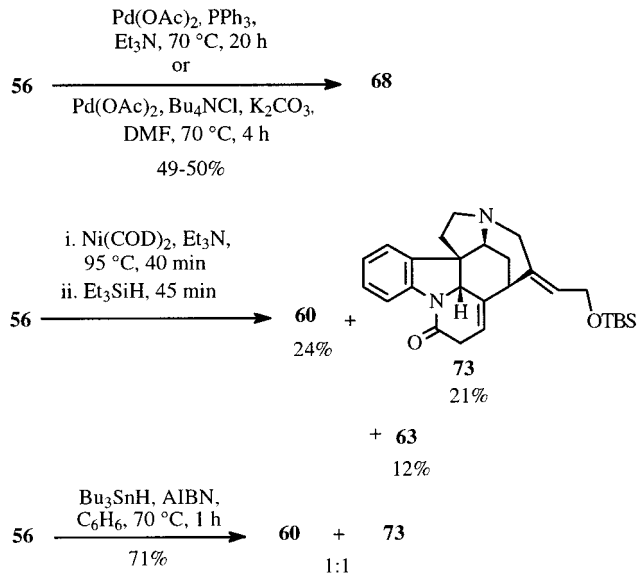
(97) Wulff, W. D.; Peterson, G. A.; Bauta, W. E.; Chan, K.-S.; Faron, K. L.; Gilbertson, S. R.; Kaesler, R. W.; Yang, D. C.; Murray, C. K. *J. Org. Chem.* **1986**, *51*, 277.

(98) (a) Crandall, J. K.; Batal, D. J.; Lin, F.; Reix, T.; Nadol, G. S.; Ng, R. A. *Tetrahedron* **1992**, *48*, 1427. (b) Aumann, R.; Trentmann, B. *Chem. Ber.* **1989**, *122*, 1977.

(99) A typical example describing an attempt at methyl sulfonyl ester formation is described in the Experimental Section.

(100) For recent reviews of the intramolecular Heck reaction see: (a) Ashimori, A.; Overman, L. E. *J. Synth. Org. Chem. Jpn.* **2000**, *58*, 718. (b) Link, J. T.; Overman, L. E. In *Metal-Catalyzed Cross Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; p 231.

Scheme 18. Formation of F Ring from **56**



DMF[101] gave a 21% yield of hexacycle **68** after 15 h at 100 °C. Attempts to flood the system with a 10-fold excess of sodium formate led to reductive elimination before cyclization to give **61** (45%). Use of tetralkylammonium formate salts[102] or Bu_3SnH[103] as alternative hydride sources failed to prevent formation of **68** in favor of **60**. Some groups have reported palladium-catalyzed conjugate additions to enones without the addition of a hydride source,[104] but generally, these systems lack readily available syn hydrogens for elimination, and their application to **56** led primarily to **68**.

The use of nickel in promoting tandem cyclization-capture sequences is known and has found successful application in the formation of piperidine and pyrrolidine rings,[105] including in Curan alkaloid systems analogous to that at hand.[105b] The success of this approach relies on the presence of a distal amino group capable of coordinating with the metal in the transient vinyl or alkylnickel species, thus preventing Ni−H β-elimination prior to trapping the intermediates with a hydride source. Reaction of **56** with $Ni(COD)_2$ in the presence of Et_3N in dry MeCN, followed by the addition of Et_3SiH, gave a mixture of the desired isostrychnine ether **60** (24%), its *Z*-isomer **73** (21%), and amine **63** (12%) (Scheme 18).[106] When, instead of Et_3SiH, an aqueous acid quench (NH_4Cl) was employed, the same mixture was obtained, albeit in a somewhat altered ratio (**60**, 21%; **73**, 11%; **63**, 18%). Silyl ether **60** displayed spectral characteristics that matched both those previously reported by Rawal[17] and those of an enantiomerically pure sample derived from natural isostrychnine.[107] Thus, isolation of **60** constitutes a formal synthesis of **1**. A radical process involving the homolytic cleavage of the carbon−iodine bond and subsequent isomerization of the vinyl radical could be responsible (vide infra), possibly initiated by electron transfer from Ni(I) formed during the reaction.[108,109]

Optimization of the Formation and Reduction of Pyridone 68. The synthesis of **68** (Scheme 18) provided the first moderately efficient entry into the desired hexacyclic system of isostrychnine (**2**). The stereoselective reintroduction of the C8 methine was all that lay between **68** and **60**. Since this task appeared soluble, some efforts were expanded in optimizing the production of **68**. Best results were obtained with the use of $Pd(OAc)_2$ and PPh_3 in Et_3N at 70 °C (Scheme 18, Table 3, entry 4) or $Pd(OAc)_2$, Bu_4NCl, and K_2CO_3 in DMF[110] at 70 °C (entry 8). Under either of these conditions, the Heck reaction proceeded in 47−50% yield. While the second gave the pyridone in relatively short reaction times (2−4 h), reactions in Et_3N or THF with PPh_3 as ligand took longer (18−22 h) and tended to return amine **63**. The amine could also be isolated from phase-transfer reactions which included added water (entry 9).[111] Various modifications of these conditions were examined. Without PPh_3, the reaction proceeded poorly in THF and amine solvents (entries 1 and 2), and other ligands [dppe, P(*o*-tolyl)$_3$] also retarded the reaction (entries 6 and 7). The use of the silver salt AgOTf failed to result in a more efficient reaction giving **68** in approximately 38% yield (entry 5).[112] Phosphine ligands were not required for the phase-transfer reaction to proceed in acceptable yield, although the reaction failed without added tetraalkylammonium catalyst (entry 12). The specific choice of phase-transfer catalyst appeared to have little effect on the reaction's outcome.

With reasonable quantities of **68** in hand, the focus became the reintroduction of the C8 methine hydrogen via a stereo- and regioselective hydride addition to the aromatic pyridone ring. In fact, reduction of a C8−C13 double bond has served as a step in a number of approaches to **1** and similar alkaloids.[10,12,14,16,113] A tactic analogous to one used by Woodward on route to **1** proved to be the most successful. Reaction of **68** with $LiAlH_4$[10,114] in THF/Et_2O (3:1) at 35 °C for 2 h led to the isolation of **60** in 39% yield. Reducing the reaction time or quantity of reducing agent failed to increase the efficiency, but running the reaction at 0 °C did increase the yield to an acceptable 54% (eq 7).

Radical-Mediated Closure of F Ring. Simultaneous with the examination of palladium-mediated methods for the formation of the piperidine ring, the potential for a radical-mediated

(101) Burns, B.; Grigg, R.; Santhakumar, V.; Sridharan, V.; Stevenson, P.; Worakun, T. *Tetrahedron* **1992**, *48*, 7297.

(102) (a) Namyslo, J. C.; Kaufmann, D. E. *Synlett* **1999**, 114. (b) Cacchi, S.; Palmieri, G. *Synthesis* **1984**, 575.

(103) (a) Taniguchi, M.; Takeyama, Y.; Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2593. (b) Schmidt, B.; Hoffmann, H. M. R. *Tetrahedron* **1991**, *47*, 9357.

(104) (a) Grubb, L. M.; Dowdy, A. L.; Blanchette, H. S.; Friestad, G. K.; Branchaud, B. P. *Tetrahedron Lett.* **1999**, *40*, 2691. (b) Bonjosch, J.; Soleé, D.; Garcia-Rubio, S.; Bosch, J. *J. Am. Chem. Soc.* **1997**, *119*, 7231. (c) Friestad, G. K.; Branchaud, B. P. *Tetrahedron Lett.* **1995**, *36*, 7047. (d) Stokker, G. E. *Tetrahedron Lett.* **1987**, *28*, 3179.

(105) (a) Solé, D.; Cancho, Y.; Llebaria, A.; Moretó, J. M.; Delgado, A. *J. Am. Chem. Soc.* **1994**, *116*, 12133. (b) Solé, D.; Cancho, Y.; Llebaria, A.; Moretó, J. M.; Delgado, A. *J. Org. Chem.* **1996**, *61*, 5895. (c) Cancho, Y.; Martín, J. M.; Martinez, M.; Llebaria, A.; Moretó, J. M.; Delgado, A. *Tetrahedron* **1998**, *54*, 1221.

(106) A trace of both the cis and trans isomers of the reduced, uncyclized alkene **61** was also observed.

(107) Reaction of isostrychnine (ref 27) with TBSOTf (1.6 equiv) and 2,6-lutidine (1.6 equiv) in CH_2Cl_2 gave a 64% yield of **60**.

(108) For a closely related example of stereochemical scrambling reported in the synthesis of the *Strychnos* alkaloid mossambine, see: Kuehne, M. E.; Wang, T. S.; Seraphin, D. *J. Org. Chem.* **1996**, *61*, 7873.

(109) Readman, S. K.; Marsden, S. P.; Hodgson, A. *Synlett* **2000**, 1628 and references therein.

(110) Jeffery, T. *Tetrahedron Lett.* **1985**, *26*, 2667.

(111) In addition to being a synthetically useful byproduct, the isolation of **63** suggested that the moderate yields were due to β-elimination of the butenyl side chain, perhaps via an intermediate palladium amide complex. The readiness of this *E*-butenyl geometry to undergo elimination has been observed previously (as noted) and may also be partly responsible for the difficulty in C14−C21 bond formation encountered in other studies which have followed similar strategies (see refs 11a, 13, 15, and 18).

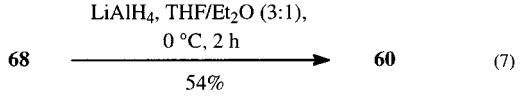
(112) Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427.

(113) (a) Vercauteren, J.; Bideau, A.; Massiot, G. *Tetrahedron Lett.* **1987**, *28*, 1267. (b) Mirand, C.; Massiot, G.; Le Men-Olivier, L.; Lévy, J. *Tetrahedron Lett.* **1982**, *23*, 1257. (c) Laronze, J. Y.; Cartier, D.; Laronze, J.; Lévy, J. *Tetrahedron Lett.* **1980**, *21*, 4441.

(114) Gallagher, T.; Magnus, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 4750.

Table 3. Heck Cyclization of Vinylic Iodide **56**

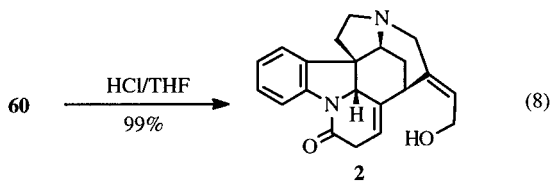
entry	catalyst (equiv)	additives (equiv)	solvent	*T* (°C) (*t* [h])	products (yield, %)
1	$Pd(OAc)_2$ (0.5)	Et_3N	THF	70 (5)	**56** (70)
2	$Pd(OAc)_2$ (0.5)	none	Et_3N	70 (20)	**56** (25), **68** (18)
3	$Pd(PPh_3)_4$ (0.2)	Et_3N	THF	65 (5)	**63** (66), **68** (17)
4	$Pd(OAc)_2$ (0.3), PPh_3 (0.6)	none	Et_3N	70 (20)	**63** (49), **68** (47)
5	$Pd(OAc)_2$ (0.2), PPh_3 (0.5)	AgOTf (1.4)	Et_3N	70 (22)	**68** (38)
6	$Pd(OAc)_2$ (0.2), P(*o*-tolyl)$_3$ (0.4)	none	Et_3N	80 (22)	**56** (90)
7	$Pd(OAc)_2$ (0.2), dppe (0.3)	none	Et_3N	80 (22)	**56** (77)
8	$Pd(OAc)_2$ (0.2)	K_2CO_3 (5), Bu_4NCl (1.5)	DMF	70 (2)	**68** (50)
9	$Pd(OAc)_2$ (0.2)	K_2CO_3 (5), Bu_4NCl (1.5)	DMF/H_2O (10:1)	70 (2)	**63** (28), **68** (42)
10	$Pd(OAc)_2$ (0.2)	K_2CO_3 (5), Bu_4NI (1.5)	DMF	70 (4)	**68** (46)
11	$Pd(OAc)_2$ (0.2)	K_2CO_3 (5), $BnBu_3NBr$ (1.5)	DMF	70 (4)	**68** (47)
12	$Pd(OAc)_2$ (0.2)	K_2CO_3 (5)	DMF	70 (3)	**68** (trace)



(7)

ring closure was examined.[115] Reaction of **56** with Bu_3SnH and Et_3B in toluene[116] at room temperature for 1 day gave primarily the deiodinated alkene **61** as a mixture of cis and trans isomers (3:7) in 41% yield, the desired hexacyclic silyl ether **60** and its *Z*-isomer **73** (1:1, 20% combined yield), and recovered **56** (18%). Fortunately, the two hexacyclic isomers were separable by careful column chromatography. Switching to benzene as solvent essentially reversed the above outcome, giving a 23% yield of **61** (2:3, cis/trans), 40% of **60** and **73** (1:1), and recovered **56** (6%). The recovery of the uncyclized reduced **61** suggested a somewhat sluggish 6-*exo*-trig closure, giving opportunity for either an intermolecular reduction of the radical by Bu_3SnH or an intramolecular 1,5-hydrogen shift from the C15 methylene. Indeed, formation of the uncyclized system could be minimized by reaction of **56** and Bu_3SnH in refluxing benzene, with AIBN as initiator, giving a 71% yield of **60** and **73**, again as a 1:1 mixture (Scheme 18).[108] While the facile isomerization of the intermediate vinyl radical, with an estimated barrier of 2 kcal/mol,[117] cannot be avoided, it was hoped that variation of the reaction conditions would affect the relative rates of ring closure of the two isomeric reactive species. However, reaction of deprotected alcohol **59** failed to improve the ratio of isomers and ruled out any steric effect of the bulky *tert*-butyl(dimethyl)silyl ether. Employment of TMS_3SiH as a radical source[118] gave an improved isomer ratio (2:1, **60**/**73**) but with a lower yield (40%). Similar results were obtained with Ph_3SnH. Finally, reaction with SmI_2, which has shown some selectivity in vinyl radical cyclizations,[119] resulted in extensive decomposition of the starting material.

As in Rawal's synthesis, deprotection of the silyl ether **60** under acidic conditions provided isostrychnine (**2**) in almost quantitative yield (eq 8).[17] The synthetic material was identical



(8)

with the natural compound by ^1H and ^{13}C NMR and TLC.[27] As mentioned above, the alcohol can be converted to **1** by the well-known base-mediated isomerization of Prelog et al.,[26] thus completing its total synthesis in racemic form.

Conclusions

The approach to **1** discussed in the final section of this paper constitutes one of the shortest reported syntheses of strychnine to date. The route to isostrychnine (**2**) involves 13 steps from propiolic acid (9 steps from tryptamine) via a radical-mediated closure of the F ring or a Ni-mediated cyclization, or 14 steps via a Heck reaction/reduction sequence, and proceeds in 2.8%, 1.9%, and 1.9%, respectively. Moreover, it is the robust nature of the cobalt-mediated [2 + 2 + 2] cycloaddition of alkynes to indoles which allows the stereo- and regioselective incorporation of a variety of functionality into the dihydrocarbazole nucleus, and the rich carbon−carbon and carbon−nitrogen bond forming chemistry of the metal-complexed and decomplexed cyclohexadiene products that ultimately provide the flexibility to design such a brief synthesis of strychnine. The effort described here serves as an example for the potential applicability of this methodology to the construction of other complex, polycyclic indole alkaloid targets.

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Supporting Information Available: Experimental procedures and spectroscopic and/or analytical details for all new compounds (PDF); X-ray crystallography data for **59** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(115) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1, 1237.
(116) Takayama, H.; Watanabe, F.; Kitajima, M.; Aimi, N. *Tetrahedron Lett.* **1997**, *38*, 5307.
(117) (a) Jiao, X.-Y.; Bentrude, W. G. *J. Am. Chem. Soc.* **1999**, *121*, 6088 and references therein. (b) Stork, G.; Baine, N. H. *J. Am. Chem. Soc.* **1982**, *104*, 2321.
(118) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188.
(119) Capella, L.; Montevecchi, P. C.; Navacchia, M. L. *J. Org. Chem.* **1995**, *60*, 7424.