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The Formal Total Synthesis of (±)-Strychnine via a Cobalt-Mediated [2 + 2 + 2]Cycloaddition

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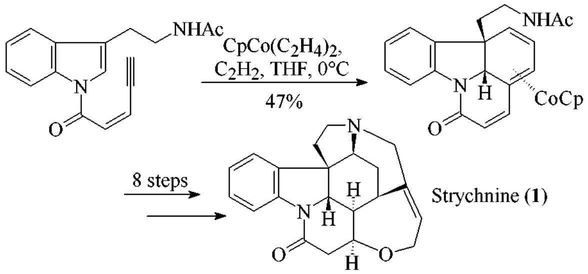
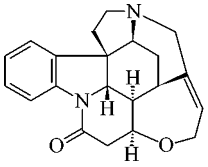
ABSTRACT



A short, highly convergent total synthesis of racemic isostrychnine, and thus strychnine, has been completed. The route involves 14 steps in the longest linear sequence and is highlighted by a cobalt-mediated [2 + 2 + 2]cycloaddition of an alkynylindole nucleus to acetylene.

Strychnine (**1**), the most famous of the *Strychnos* alkaloids and a commonly used rat poison, has long held the fascination of organic chemists. The elucidation of the structure of this heptacycle took more than a century, and its construction by R. B. Woodward, first reported in 1954, remains a landmark in organic synthesis.[1] Since then, several syntheses of **1**,[2] including those of both enantiomers,[3] have been achieved. Indeed, the inherent complexity of strychnine, with its seven rings and six stereocenters displayed across a framework of only 24 atoms, has resulted in the continued appeal of the alkaloid as a target on which to demonstrate the utility of novel synthetic methods.



1

We approached the total synthesis of **1** as part of our ongoing work in expanding the scope and utility of the cobalt-mediated [2 + 2 + 2]cycloaddition reaction.[4] The ability of cyclopentadienyl cobalt to effect the cycloaddition of three unsaturated functionalities with a high degree of chemo-, regio-, and stereoselectivity has resulted in the assembly of a number of complex natural products.[5] The

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[1] (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.

[2] Racemic syntheses of **1**: (a) Magnus, P.; Giles, M.; Bonnert, R.; Kim, C. S.; McQuire, L.; Merritt, A.; Vicker, A. *J. Am.. Chem. Soc.* **1993**, *115*, 8116. (b) Stork, G. Reported at the Ischia Advanced School of Organic Chemistry, Ischia Porto, Italy, September 21, 1992. (c) Kuehne M. E.; Xu, F. *J. Org. Chem.* **1993**, *58*, 7490. (d) Rawal, V. H.; Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685.

[3] Enantioselective syntheses of **1**: (a) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1995**, *117*, 5776. (b) Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1998**, *63*, 9427. (c) Solé, D.; Bonjoch, J.; García-Rubio, S.; Peidró, E.; Bosch, J. *Angew. Chem., Int. Ed.* **1999**, *38*, 395. (d). Solé, D.; Bonjoch, J.; García-Rubio, S.; Peidró, E.; Bosch, J. *Chem. Eur. J.* **2000**, *6*, 655.

[4] For an earlier report of our efforts toward the synthesis of **1**, see: Grotjahn, D. B.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1990**, *112*, 5653.

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wide variety of functionalities which participate in this reaction include a number of aromatic heterocyclic double bonds, such as those of pyrrole,[6a] imidazole,[6b] furan, thiophene,[6c] and benzofuran.[6d] More pertinently, the indole nucleus is also active in these cyclizations, providing an efficient entry into polycyclic, alkaloid-like structures, and suggesting its use in a cobalt-mediated approach to **1**. As shown in Figure 1, indoles, including those substituted at C-3, can be cyclized, both intra- and intermolecularly, with a wide variety of alkynes to yield functionalized products in moderate to good yields.[7]

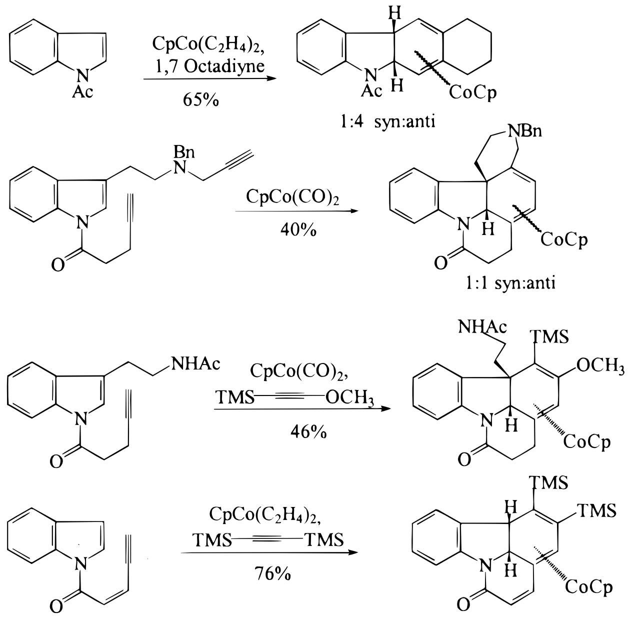
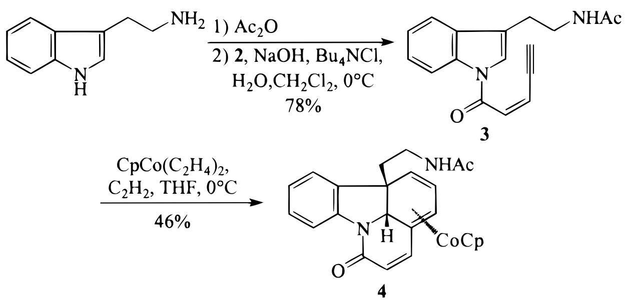


Figure 1. Some cobalt-mediated [2 + 2 + 2]cyclizations of the indole nucleus.

Our strategy begins with tryptamine, which is converted into the tetracyclic core of strychnine as shown in Scheme 1. The commercial starting material was first acylated at its primary amino group with acetic anhydride[8] and then at the indole nitrogen with the enynoyl chloride **2** under phase-transfer conditions, with *in situ* deprotection of the alkyne, to afford the N-protected enynoylindole **3**.[9]

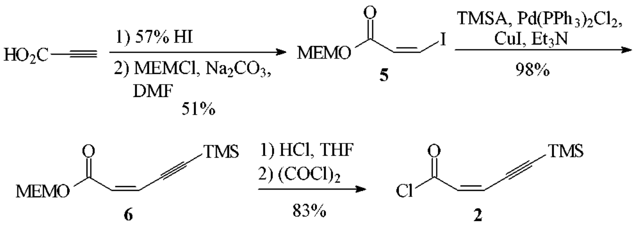
Scheme 1



The production of **3** set the stage for a partly intramolecular [2 + 2 + 2]cycloadditon which would construct the carbazole core of **1**. Thus, in THF solution, **3** was converted to tetracyclic lactam **4** in the presence of $CpCo(C_2H_4)_2$[10] and acetylene gas.[11] The reaction proceeded with complete selectivity, producing **4** in 47% yield as a single diastereomer.[12]

Synthesis of acid chloride **2** began with propiolic acid and is outlined in Scheme 2. The acid was selectively iodinated[13] to the *cis* isomer and then esterified with the methoxyethoxymethyl group to afford **5**. Protection of the carboxy function proved to be necessary for the success of the subsequent Sonogashira-type coupling of **5** with trimethysilylacetylene. Acidic hydrolysis of the resulting ester **6** afforded the acid,[14] which, on reaction with oxalyl chloride, was converted to acid chloride **2**. This five-step sequence proceeds in 42% overall yield to afford multigram quantities of **2**.

Scheme 2



The synthesis of strychnine continued with the organometallic intermediate **4** as shown in Scheme 3. The exocyclic nitrogen was deprotected with KOH in boiling methanol−water, highlighting the use of the CpCo diene moiety as a protecting group. Closure of the pyrrolidine ring occurred

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

(6) (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.

(7) (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.

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

(9) (a) Illi, V. O. *Synthesis* **1979**, 397. (b) Oldroyd, D. L.; Weedon, A. C. *J. Org. Chem.* **1994**, *59*, 1333.

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

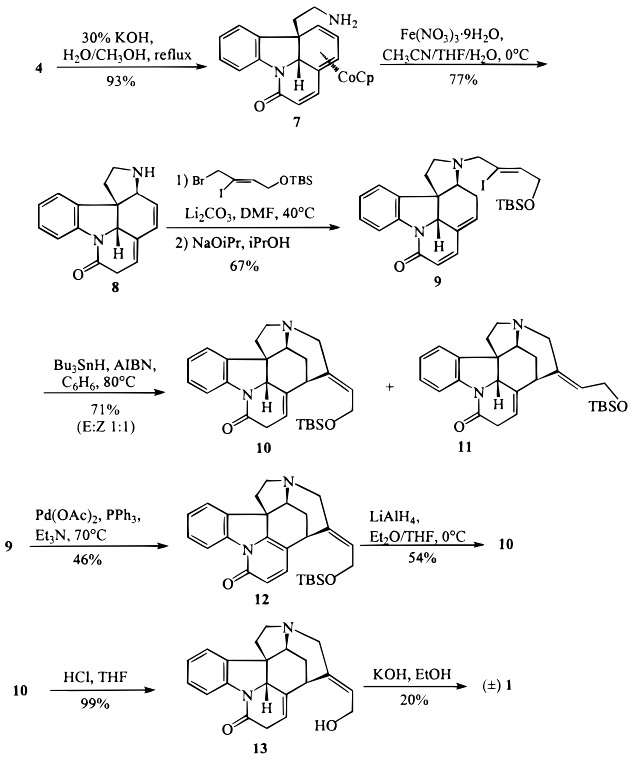
(11) Critical to the success of this reaction is the addition rate of the cobalt reagent, the initial concentration of **3** (0.05 M), the temperature (0 °C), and the rate of the acetylene addition, which must be moderated by a concomitant nitrogen or argon purge of the reaction mixture.

(12) The primary byproducts of this reaction, isolated in 20−30%, yield are the *cis*- and *trans*-cinnamic amides of *N*-acetyltryptamine. Presumably, these arise from the cyclization of the terminal acetylene of enyne **3** with two acetylene molecules and subsequent stereoequilibriation.

(13) Moss, R. A.; Wilk, B.; Krogh-Jespersen, K.; Westbrook, J. D. *J. Am. Chem. Soc.* **1989**, *111*, 6729.

(14) Abarbri, M.; Parrain, J.-L.; Cintrat, J.-C.; Duchêne, A. *Synthesis* **1996**, 82.

Scheme 3



upon oxidative demetalation of **7** with iron(III) to afford pentacycle **8** in a formal [1,8]-conjugate addition of the amine function to the unsaturated lactam π-system. Alkylation of the amine nitrogen with (*Z*)-1-bromo-4-[(*tert*-butyldimethylsilyl)oxy]-2-iodobut-2-ene,[2d] followed by base-catalyzed isomerization of the diene unit into conjugation with the amide carbonyl, afforded vinyl iodide **9**.

The vinyl iodide functionality in **9** presents a number of opportunities for the formation of the desired piperidine ring, including, metal−iodide exchange/conjugate addition,[15] Pd-mediated Heck/anion capture sequences,[16] and radical-mediated closure. By far the most successful of these methods was the latter. Thus, reaction of **9** with Bu_3SnH and AIBN generated the desired hexacyclic silyl ether **10**, previously reported by Rawal in his synthesis of **1**,[2d] as a 1:1 mixture with its *Z*-isomer **11** in 71% overall yield. Apparently arising from the extremely facile isomerization of the intermediate vinyl radical before the desired 6-*exo-trig* ring-closure,[17] the 1:1 ratio of *E*/*Z* isomers could not be further optimized.[18] However, the two isomers were separated without difficulty by column chromatography. An alternative, two-step cyclization procedure involved an intramolecular Heck reaction of **9** to form, following β-elimination of the C-8 hydrogen and aromatization, the pyridone **12**.[2d] This compound could be selectively reduced by $LiAlH_4$ to furnish **10**.[19]

As in Rawal's synthesis, deprotection of the silyl ether under acidic conditions provided isostrychnine (**13**) in almost quantitative yield. Identical by ^{1}H and ^{13}C NMR, TLC, and mp with the natural compound, the alcohol can be converted to **1** by the well-known base-mediated isomerization of Prelog et al.[20]

In conclusion, we have completed the shortest reported synthesis of the complicated strychnine framework to date. This synthesis serves to demonstrate the continued utility of the cobalt-mediated [2 + 2 + 2]cycloaddition reaction in the construction of complex natural products.

Acknowledgment. We thank the NSF (CHE-0071887 and a predoctoral fellowship for M.J.E.) for their generous support. We also thank Professor Viresh Rawal for providing experimental details for the synthesis of (*Z*)-1-bromo-4-[(*tert*-butyldimethylsilyl)oxy]-2-iodobut-2-ene.

Supporting Information Available: Detailed experimental procedures and complete spectroscopic and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) These include reaction with alkyllithium reagents, attempted formation of cuprates or Grignard intermediates, the use of $NiCl_2/CrCl_2$, and activated copper and zinc reagents. Full details of the results of this synthetic study are to be reported elsewhere.

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

(17) Stork, G.; Baine, N. H. *J. Am. Chem. Soc.* **1982**, *104*, 2321.

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

(19) Interestingly, this step is quite similar to a reduction of a late-stage pyridone intermediate in Woodward's original synthesis of strychnine (ref 1b). He attributes the selectivity to the directing effect of a free hydroxyl present in the substrate, while we rationalize our result by the attack of the hydride from the less-hindered *si* face.

(20) Prelog, V.; Battegay, J.; Taylor, W. I. *Helv. Chim. Acta* **1948**, *31*, 2244. This ring closure step was also used as the last step in the strychnine syntheses of Woodward (ref 1), Kuehne (ref 2c), and Rawal (ref 2d).