A Short, Stereocontrolled Synthesis of Strychnine†

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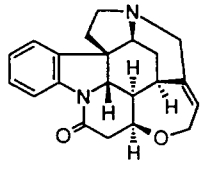
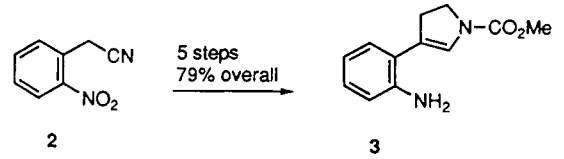
Summary: Strychnine has been synthesized by a short, highly stereocontrolled route that involves the efficient transformation of commercially available 2-nitrophenylacetonitrile into isostrychnine, a known precursor to strychnine.

It was with words of awe and excitement that R. B. Woodward described "Strychnine!" (1), a heptacyclic alkaloid that has fascinated organic chemists for centuries.[1] Well over 100 man years of effort, related through several hundred publications, was required to secure the correct structure of this natural product.[2,3] Soon after this achievement, in 1954 Woodward reported a brilliant synthesis of strychnine. Remarkably, it took nearly 40 years to repeat this feat, despite considerable effort from many groups. Over the past 2 years, however, several groups have reported solutions to strychnine.[4] We report here a simple solution to the structural challenge posed by strychnine



1: strychnine

The present synthesis highlights the strategy that we have developed for the synthesis of the pentacyclic *strychnan* skeleton.[5] Thus, commercially available *o*-nitrophenylacetonitrile was transformed into pyrroline **3**, having an aniline unit at the 3-position. This five-step sequence proceeded in high overall yield and, more importantly, could be performed on a large scale, so that up to 25 g of **3** could be prepared with ease.



2 3

Pyrroline **3** was converted into strychnine as described in Scheme 1. In the presence of an excess of unsaturated aldehyde **4**,[6] pyrroline **3** was transformed quantitatively into the expected imine.[8] Upon quenching the reaction mixture with excess methyl chloroformate and diethylaniline, the desired diene–carbamate **5** was obtained in high yield. Diene **5** underwent a smooth intramolecular cycloaddition upon heating in benzene in a sealed tube at 185–200 °C. The reaction gave in quantitative yield and with complete stereocontrol the desired tetracycle **6**, with three of strychnine's stereocenters correctly set. The ester and the two carbamates could then all be demethylated at once by heating **6** with an excess of iodotrimethylsilane. Upon quenching the reaction mixture with methanol, to hydrolyze the presumed intermediate trimethylsilyl carboxylates, pentacyclic lactam **7** was obtained in good yield. The efficiency of this transformation is remarkable since formally seven different reactions are taking place.

In preparation for the bridged ring, the secondary amine **7** was alkylated by treating it with allylic bromide **8**[9] in acetone–DMF (5:1) in the presence of K_2CO_3. The resulting vinyl iodide **9** was now set for the pivotal C–C bond-forming reaction. Under the Jeffrey modification of the Heck reaction conditions, **9** was smoothly transformed into a hexacyclic *strychnan* in 74% yield.[10] Removal of the silyl protecting group under acidic conditions afforded isostrychnine (**10**) in quantitative yield.[11] The final step, a base-mediated isomerization of isostrychnine to strychnine, was carried out as described by Prelog et al. during the course of structure elucidation work.[12]

The strychnine synthesis described here is noteworthy for the quickness with which the framework is assembled, the total control of all stereocenters, and the high overall yield of all new steps.

† Dedicated with affection and respect to Professor Michael P. Cava, whose original work with Woodward provided the inspiration for this project.

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(1) (a) Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *J. Am. Chem. Soc.* **1954**, *76*, 4749. (b) Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *Tetrahedron* **1963**, *19*, 247.

(2) For example, during the 130 years between the isolation and structure elucidation, Sir Robert Robinson's group alone published over 250 communications on the subject. Hermann Leuchs contributed another 125 papers. See reference 1. For an extensive review of the chemistry of strychnine, see: Smith, G. F. In *The Alkaloids*; Manske; R. H. F., Ed.; Academic Press: New York, 1965; pp 591–671.

(3) Review: (b) Husson, H. P. In *Indoles: Monoterpenes Indole Alkaloids*; Saxton, J. E., Ed.; Wiley: New York, 1988; Chapters 1 and 7.

(4) (a) Magnus, P.; Giles, M.; Bonnert, R.; Johnson, G.; McQuire, K.; Deluca, M.; Merrit, A.; Kim, C. S.; Vicker, N. *J. Am. Chem. Soc.* **1993**, *115*, 8116 and references cited therein. After we had completed the synthesis of isostrychnine, two other strychnine syntheses were reported: (b) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1993**, *115*, 9239. (c) Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1993**, *58*, 7490. (d) In addition, Professor Stork (Columbia University) has described a successful route at a meeting (see ref 4 b).

(5) (a) Rawal, V. H.; Michoud, C.; Monestel, R. F. *J. Am. Chem. Soc.* **1993**, *115*, 3030. For earlier model studies, see: (b) Rawal, V. H.; Michoud, C. *J. Org. Chem.* **1993**, *58*, 5583. (c) Rawal, V. H.; Michoud, C. *Tetrahedron Lett.* **1991**, *32*, 1695 and references cited therein.

(6) Prepared from (*Z*)-2-iodo-2-buten-1-ol (see ref 5c): (a) methyl acrylate (10 equiv), Bu_3SnCl (0.2 equiv), $NaBH_4$, EtOH, *hν* (70%, see ref 7); (b) PDC, CH_2Cl_2, Celite, rt (89%).

(7) (a) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1975**, *40*, 2554. (b) Gerth, D. B.; Giese, B. *J. Org. Chem.* **1986**, *51*, 3726.

(8) Initially, the imine was isolated and purified by flash chromatography.

(9) Prepared from the mono-THP ether of butynediol: (a) RedAl, Et_2O, 0 °C; I_2; (b) TBS-Cl, imidazole; (c) $MgBr_2$, Et_2O, rt; (d) Ph_3P, NBS.

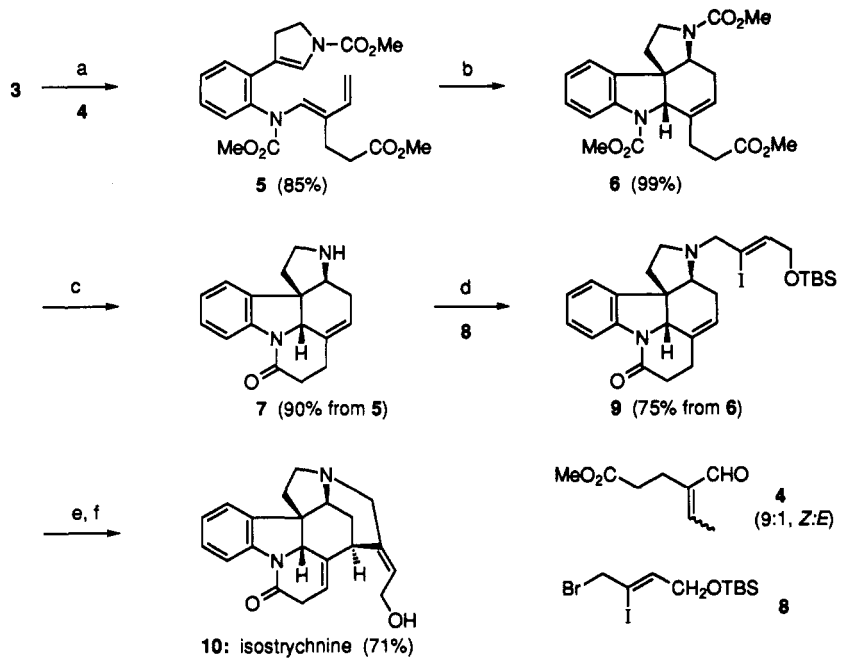
(10) Jeffery, T. *Tetrahedron Lett.* **1985**, *26*, 2667. For a recent review on the Heck reaction, see: Heck, R. F. Vinyl Substitution with Organopalladium Intermediates. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1992; Vol. 4, p 842.

(11) Yields are reported for isolated compounds. New compounds showed ^1H NMR, ^{13}C NMR, IR, and high-resolution mass spectra in complete accord with their assigned structure.

(12) Prelog, V.; Battegay, J.; Taylor, W. I. *Helv, Chim. Acta* **1948**, *31*, 2244. This ring closure was also used as the last step in Woodward's strychnine synthesis (see ref 1) and more recently in Kuehne's synthesis (see ref 4c).

0022-3263/94/1959-2685$04.50/0

Scheme 1[a]



[a] Key: (a) RCHO (4) neat, rt; then $ClCO_2Me$, $PhNEt_2$; (b) PhH, 185 °C, 4 h, (c) TMS-I (10 equiv), $CHCl_3$, reflux, 5 h; MeOH quench, Δ, 6 h; (d) 8, acetone–DMF (5:1), K_2CO_3; (e) $Pd(OAc)_2$ (0.3 equiv), Bu_4NCl, DMF, K_2CO_3, 70 °C, 3 h; (f) 2 N HCl, THF.

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Supplementary Material Available: Experimental procedures and copies of NMR spectra (16 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.