General Strategy for the Stereocontrolled Synthesis of *Strychnos* Alkaloids: A Concise Synthesis of (±)-Dehydrotubifoline

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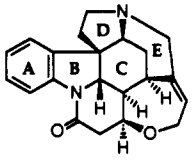
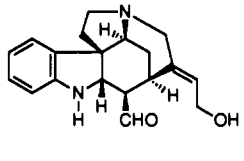
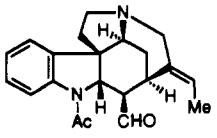
The *Strychnos* alkaloids form a large family of structurally intricate compounds that have powerful physiological activity.[1] These alkaloids share a common topology characterized by the pentacyclic strychnan framework (see representative examples **1–4**), in which rings C and E are joined by a bridged juncture and ring E bears an exocyclic olefin of defined geometry. The



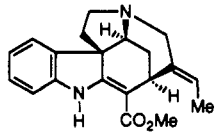
1: strychnine



2: desacetyldiaboline (Wieland-Gumlich aldehyde)



3: isoretulinal

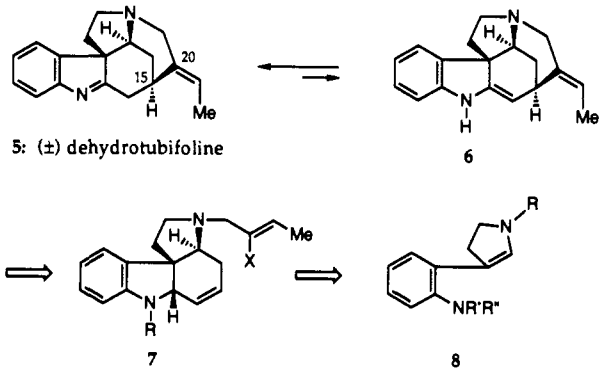


4: akuammicine

stereoselective synthesis of these alkaloids remains a considerable challenge.[2,3] We have formulated a general, concise strategy that addresses the structural challenges posed by most members of the *Strychnos* alkaloids and specifically solves the difficult problem of controlling the exocyclic olefin geometry.[2] In this communication we demonstrate the successful implementation of this strategy through the stereocontrolled synthesis of (±)-dehydrotubifoline (**5**).[4]

Our synthetic plan for (±)-dehydrotubifoline (**5**), which possesses the key structural features of the strychnan skeleton, was predicted on the expectation that this molecule exists as an equilibrium mixture of imine and enamine (**6**) tautomers, greatly favoring the former (Scheme I). The key retrosynthetic disconnection, then, was cleavage of the C_{15}–C_{20} bond, which led to great simplification of the strychnan skeleton. In the actual

Scheme I



5: (±) dehydrotubifoline

6

7

8

synthesis (**7** → **6**) this strategic bond could be formed by an intramolecular Heck reaction, a process expected to be facilitated by the axially oriented pyrrolidine nitrogen.[5,6] The tetracyclic core of **7** could be constructed by an intramolecular Diels–Alder reaction.

The initial objective was to develop an effective route to the 3-aryl-δ_2-pyrroline unit (Scheme II). Following a strategy similar to that developed by Stevens,[7] commercially available 2-nitrophenylacetonitrile was reacted with 1,2-dibromoethane and base under phase-transfer conditions[8] to afford the expected cyclopropane in 96% yield (Scheme II).[9] Selective reduction of the nitrile using DIBAL-H followed by an acidic quench gave the desired aldehyde **10** in quantitative yield.[10] Condensation of the aldehyde with benzyl amine gave an imine that was directly submitted to the cyclopropyl iminium ion rearrangement conditions. The major product using Stevens's original procedure (neat imine, catalytic NH_4Cl, 120 °C, argon) was the 3-aryl-substituted pyrrole, resulting from dehydrogenation of the desired rearranged product. On the other hand, when the reaction was carried out in acetonitrile, the desired pyrroline was obtained in 89% yield. Problems were encountered on carrying out this procedure on a large scale, which prompted us to investigate new methods for this transformation. We discovered that the desired rearrangement is promoted at a much lower temperature and in excellent yield using catalytic amounts of Me_3SiCl and NaI in DMF (60 °C, 3 h).[11] The chemistry outlined here enabled us to prepare the 3-aryl-δ_2-pyrroline derivative **12** on >25 g scale.

In preparation for the cycloaddition reaction, enamine **12** was converted to the enecarbamate by reaction with methyl chloroformate (acetone, room temperature (rt), 8 h, 90%).[12] Chemoselective reduction of the nitro group under transfer hydrogenation conditions (10% Pd/C, HCO_2NH_4Cl, MeOH, rt)[13] gave the aniline derivative **13** (95%). The required diene moiety was then assembled by condensation of the aniline with crotonaldehyde,

(1) Reviews: (a) Bosch, J.; Bonjoch, J. Pentacyclic *Strychnos* Alkaloids. In *Studies in Natural Products Chemistry*; Rahman, A., Ed.; Elsevier: Amsterdam, 1988; Vol. 1, p 31. (b) Husson, H. P. In *Indoles: Monoterpenes Indole Alkaloids*; Saxton, J. E., Ed.; Wiley: New York, 1988; Chapters 1 and 7.

(2) Strychnine syntheses: (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. After a span of nearly 40 years, a second synthesis of strychnine was recently reported: (c) Magnus, P.; Giles, M.; Bonnet, R.; Kim, C.; McQuire, L.; Merrit, A.; Vicker, N. *J. Am. Chem. Soc.* **1992**, *114*, 4403.

(3) For recent synthetic approaches to *Strychnos* alkaloids, see: (a) Teuber, H. J.; Tsaklakidis, C.; Bats, J. W. *Liebigs Ann. Chem.* **1992**, *5*, 461. (b) Kraus, G. A.; Bougie, D. *Synlett* **1992**, *4*, 279. (c) Nkiliza, J.; Vercauteren, J.; Léger, J. M. *Tetrahedron Lett.* **1991**, *32*, 1787. (d) Kuehne, M. E.; Frasier, D. A.; Spitzer, T. D. *J. Org. Chem.* **1991**, *56*, 2696. (e) Kraus, G. A.; Thomas, P. J.; Bougie, D.; Chen, L. *J. Org. Chem.* **1990**, *55*, 1624. (f) Grotjahn, D. B.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1990**, *112*, 5653. (g) Amat, M.; Linares, A.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 6299 and references therein.

(4) The total synthesis of (±)-dehydrotubifoline was recently reported: (a) Fevig, J. M.; Marquis, R. W., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5085. Also see: (b) Harley-Mason, J.; Crawley, G. C. *J. Chem. Soc., Chem. Commun.* **1971**, *93*, 685. (c) Takano, S.; Hirama, M.; Ogasawara, K. *Tetrahedron Lett.* **1982**, *23*, 881.

(5) For a recent review on the Heck reaction, see: Heck, R. F. Vinyl Substitution with Organopalladium Intermediates. In *Comprehensive Organic Synthesis*; Trost, B., Ed.; Pergamon Press, 1992; Vol. 4, p 842.

(6) For model studies leading to the strategy presented here, see: Rawal, V. H.; Michoud, C. *Tetrahedron Lett.* **1991**, *32*, 1695 and references therein.

(7) Reviews: (a) Stevens, R. V. *Acc. Chem. Res.* **1977**, *10*, 193. (b) Boeckman, R. K.; Walters, M. A. The Scope and Mechanism of the Cyclopropyliminium Ion Rearrangement and Applications to Alkaloid Synthesis. In *Advances in Heterocyclic Natural Product Synthesis*; Pearson, W. H., Ed.; JAI Press: New York, 1990; Vol. 1, p 1.

(8) A full equivalent of *n*-Bu_4NBr was required to obtain high yields.

(9) 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.

(10) Aldehyde **2** is not stable on silica gel. The product isolated after extraction with ether was found to be >95% pure.

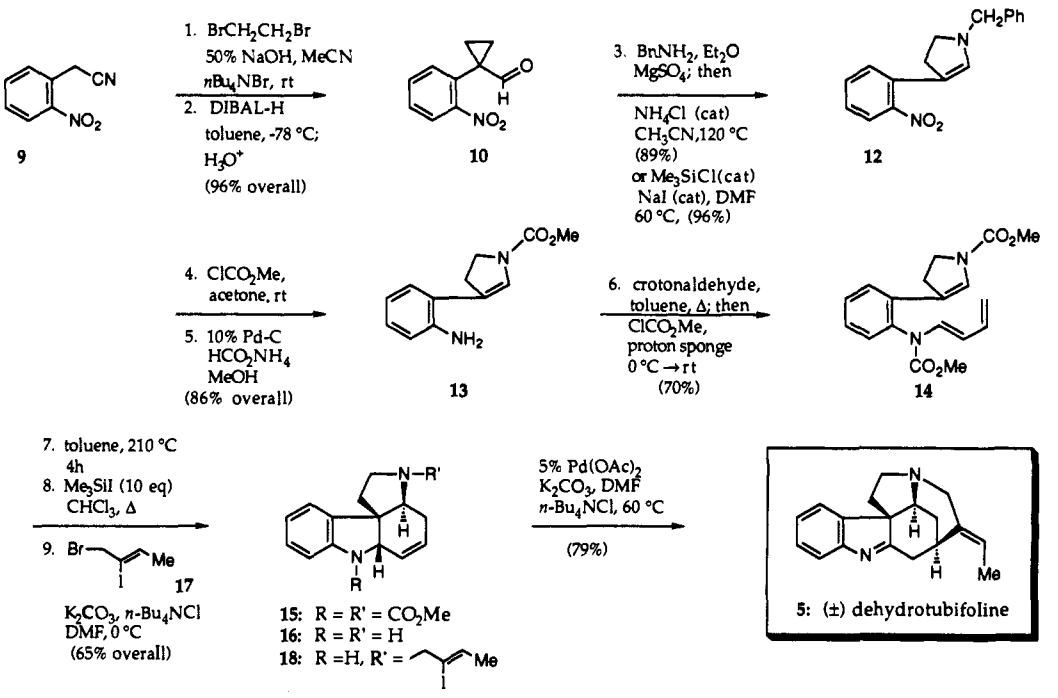
(11) We are presently investigating the scope of this procedure.

(12) To our knowledge, this is the first example of an alkyl chloroformate-promoted dealkylation of an enamine. For an example of debenzylation of tertiary amines by chloroformates, see: (a) Hanessian, S.; Faucher, A. M.; Léger, S. *Tetrahedron* **1990**, *46*, 231. (b) Rawal, V. H.; Jones, R. J.; Cava, M. P. *J. Org. Chem.* **1987**, *52*, 19.

(13) Ram, S.; Ehrenkaufer, R. E. *Tetrahedron Lett.* **1984**, *25*, 3415.

0002-7863/93/1515-3030$04.00/0

Scheme II



followed by trapping with methyl chloroformate (toluene, rt, proton sponge, 8 h).[14]

The nature of substrate **14**, in which both the diene and the dienophile are electron rich, prompted us to investigate the [4 + 2] cycloaddition reaction catalyzed by cation radical salts.[15] Unfortunately, triene **14** decomposed in the presence of a catalytic amount of $Ar_3N^+ \cdot SbCl_6$ (Ar = *p*-BrPh; 0.1 equiv, CH_2Cl_2, 0 °C). The desired transformation can, however, be accomplished thermally (toluene, 210 °C, steel bomb), affording tetracycle **15** in excellent yield as a single diastereomer.[16] This tetracycle should prove to be quite versatile as it can serve as a common intermediate for the synthesis of many other *Strychnos* alkaloids and represents an integral part of *Aspidosperma* family of alkaloids.

The two carbomethoxy groups on **15** can be removed cleanly using an excess of Me_3SiI ($CHCl_3$, reflux, 4 h, 99%).[17] The elements of the bridged piperidine ring were then introduced by chemoselective alkylation of diamine **16** with allylic bromide **17**[18] (K_2CO_3, *n*-Bu_4NCl, DMF, 0 °C). The critical ring closure was promoted by a Heck reaction [5% $Pd(OAc)_2$, 5 equiv of K_2CO_3, 1 equiv of *n*-Bu_4NCl, DMF, 60 °C],[19] a process which preserved the integrity of the double bond stereochemistry. The anticipated enamine → imine tautomerization took place to give, after chromatographic purification (95:5 ether–diethylamine), the pentacyclic strychnan (±)-dehydrotubifoline as a beige powder, mp 78 °C dec.[20]

The synthesis of (±)-dehydrotubifoline described here represents a general solution to the structural challenge posed by *Strychnos* alkaloids. The strategy, which calls for the formation of five carbon–carbon bonds and four rings, has been executed in 10 steps with complete stereocontrol and high overall yield (>25%). We are currently investigating the use of this route for the synthesis of more complex members of the *Strychnos* family (e.g., **1–4**).

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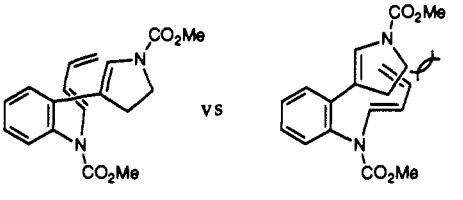
(14) Oppolzer, W.; Bieber, L.; Francotte, E. *Tetrahedron Lett.* **1979**, 981. The procedure recommends the use of diethylaniline. We found the reaction to be much cleaner using Proton Sponge (Aldrich) as the base.

(15) For a review on cation radical-promoted cycloadditions, see: Bauld, N. *Tetrahedron* **1989**, *45*, 5307.

(16) The diastereomer obtained arises from the exo transition state, in which the nonbonding interactions are minimized.



(17) Olah, G. A.; Narang, S. C. *Tetrahedron* **1982**, *38*, 2225.

(18) Bromide **17** was prepared from the corresponding alcohol (ref 6) in 84% yield (NBS, PPh_3, CH_2Cl_2).

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

(20) The ^1H NMR and ^{13}C NMR spectra of our sample correlated well with those kindly provided by Professor L. E. Overman (University of California, Irvine). See ref 4a. We thank Professor Overman for sending us the spectra.