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First Total Synthesis of (±)-Strychnofoline via a Highly Selective Ring-Expansion Reaction

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Strychnofoline belongs to a class of natural products isolated from the leaves of *Strychnos usambarensis*,[1] which displays antimitotic activity against cultures of mouse melanoma and Ehrlich tumor cells with strychnofoline showing the highest activity.[2] A prominent structural feature of these and related spirotryprostatin alkaloids[3] is the presence of a spiro[pyrrolidin-3,3′-oxindole] nucleus. Because of the biological activity of these molecules as well as the synthetic challenges presented by their complex architecture, we have embarked on a program that aims at developing efficient strategies toward their preparation.[4,5] In this communication, we describe our efforts along these lines which have led to the first total synthesis of (±)-strychnofoline (Scheme 1). A key feature of the strategy delineated is the convergent assembly of the core through the ring-expansion reaction of a spiro-[cyclopropan-1,3′-oxindole] and a cyclic imine.

In the context of complex molecule syntheses, preparation of spiro[perhydroindolizine-oxindoles] has been effected following three general strategies. The first was reported in the total synthesis of the related antineoplastics, wherein condensation of a 2-oxytryptamine with an aldehyde afforded an imine that subsequently participated in an intramolecular Mannich reaction.[6a−e] In the parallel, alternate approach, the oxidative rearrangement of yohimbinoids provided access to oxindole alkaloids.[6f,g] The third approach reported to date is found in the elegant total synthesis of pseudotabersonine, wherein the analogous spirofused quinolizidine-oxindole ring system was formed by aza Diels−Alder reaction of an imine and diene.[7]

In a preliminary study, we have reported a novel ring-expansion reaction of a spiro[cyclopropan-1,3′-oxindole] with a range of simple, unfunctionalized imines to furnish spiro[pyrrolidin-3,3′-oxindoles][4] (Scheme 2). Although this reaction proved diastereoselective, the critical issue of stereocontrol as a function of substitution on the imine was left unanswered. In this respect, the question of whether stereoselectivity could be derived from the imine fragment would be crucial to address if the method was to be effective for asymmetric synthesis of more complex structures. Investigations aimed at the total synthesis of strychnofoline thus offered an opportunity to address this critical issue. The approach devised for strychnofoline posed an additional synthetic challenge: access to and preparative use of cyclic imines such as **11** (Scheme 3). We found that routes involving generation of an amino aldehyde which would subsequently undergo cyclocondensation to give imine proved futile, as imines prepared under such conditions underwent oligomerization. After considerable experimentation, we found a new mild, convenient method that accesses the requisite cyclic imine from Boc-protected enamine **9** upon treatment with TMSOTf/NEt_3 as described below.

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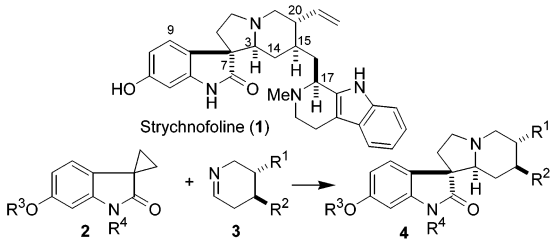
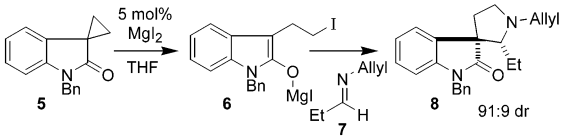
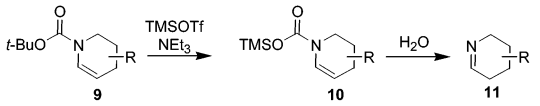
Scheme 1



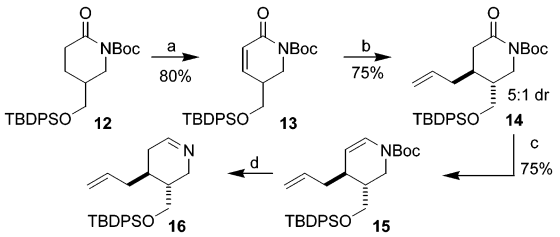
Scheme 2



Scheme 3



Scheme 4 [a]



[a] (a) (i) PhSeCl, LHMDS, THF, −78 °C; (ii) H_2O_2, EtOAc, room temperature. (b) CuBr·SMe_2, allyl MgCl, TMSCl, THF, −78 °C. (c) (i) DIBAL−H, THF, −78 °C; (ii) aqueous HCl, CH_2Cl_2, room temperature. (d) TMSOTf, NEt_3, CH_2Cl_2, −20 °C.

The synthesis of imine **16** commences with **12** (Scheme 4).[8] Treatment of the enolate of **12** with PhSeCl, followed by H_2O_2, furnished unsaturated lactam **13** (80%). Treatment of **13** with CuBr·SMe_2/AllylMgCl gave **14** (75%) as a 5:1 mixture of inseparable diastereoisomers.[9] Reduction of **14** and the conversion of the corresponding lactamol to enamine **15** (1 N aqueous HCl/CH_2Cl_2, 5 min, 75% yield) permitted facile isolation of a single diastereoisomer after chromatography on silica gel.[10] Mild cleavage of the Boc-group (NEt_3, TMSOTf, −20 °C with aqueous workup) converted enamine **15** into imine **16**. This cyclic imine **16** was directly employed without purification in the subsequent ring-expansion reaction because of its instability. Thus, heating of **17**[11] with **16** in THF in the presence of MgI_2 at 80 °C for 12 h afforded key intermediate **18** as a single diastereomer in 55% yield over two steps (Scheme 5). The relative stereochemistry between the

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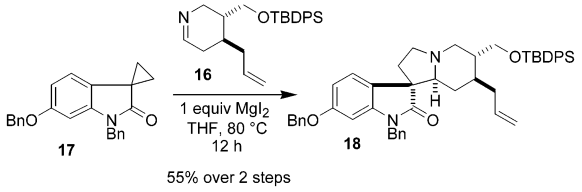
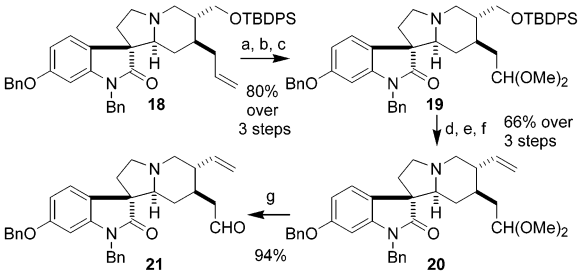
Scheme 5

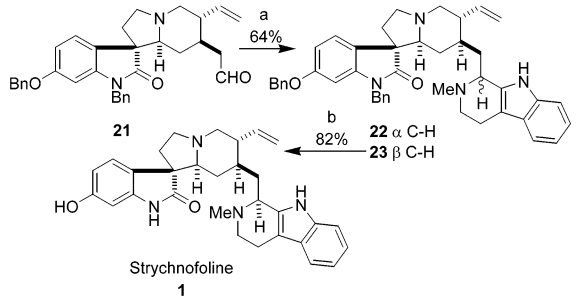


Scheme 6 [a]



[a] (a) NMO, OsO_4, H_2O, dioxane, *t*-BuOH, room temperature. (b) $NaIO_4$, H_2O, *t*-BuOH, dioxane, room temperature. (c) *p*-TsOH, MeOH, $CH(OMe)_3$, room temperature. (d) TBAF, THF, room temperature. (e) IBX, DMSO, room temperature. (f) *t*-BuOK, Ph_3PMeBr, THF, room temperature. (g) 10% aqueous HCl, acetone, room temperature.

Scheme 7 [a]



[a] (a) *N*-Methyltryptamine, AcOH, toluene, 80 °C. (b) Na, NH_3, THF, *t*-BuOH, −78 to −45 °C.

two newly formed stereocenters at C-3 and C-7 was confirmed by ^{1}H NMR NOE studies and ultimately through X-ray crystallographic analysis of **20** (vide infra).[12] Although the underlying stereodetermining elements leading to the formation of **18** are difficult to discern at present, the stereochemical outcome is congruent with the known preferences in related alkaloids such as rhynchophylline and isorhynchophylline.[13] For these, the observed stereochemistry has been suggested to result from thermodynamic considerations. In this regard, analysis of diastereomers epimeric at C-3 reveals that destabilizing axial interactions would be unavoidable, and diastereomers epimeric at C-7 are suggested to be precluded because of ensuing unfavorable interactions between the nitrogen and carbonyl lone pairs.

Elaboration of the key intermediate to the natural product commenced with conversion of alkene **18** to ketal **19** (Scheme 6). Thus, oxidative cleavage of **18** (OsO_4, $NaIO_4$) furnished the corresponding aldehyde, which was protected ($CH(OMe)_3$ and *p*-TsOH, MeOH) to afford dimethoxyacetal **19** (80%, over three steps). Desilylation with TBAF, followed by an oxidation with IBX in DMSO and Wittig olefination, provided **20** in 66% overall yield (three steps).[14] Deprotection of the acetal with aqueous HCl in acetone provided aldehyde **21** (94%). Completion of the natural product necessitated coupling the *N*-methyl carboline side chain. In this respect, Pictet Spengler reaction[15] of aldehyde **21** and *N*-methyl-tryptamine using AcOH in toluene at 80 °C afforded a diastereomeric mixture of products **22** and desired **23** nonselectively (1.5:1) in a combined yield of 64%.[16] Deprotection of **23** (Na in NH_3, THF, and *t*-BuOH warming from −78 to −45 °C) afforded (±)-strychnofoline (**1**) in 82% yield (Scheme 7). The synthetic material isolated was in all respects identical to the material from natural sources by TLC, mass spectrometry, ^{13}C NMR, and ^{1}H NMR spectroscopy.

In summary, we have reported an efficient synthesis of the antitumor alkaloid (±)-strychnofoline. Key to the development of the highly convergent strategy delineated is the coupling of a cyclic imine with spiro[cyclopropan-1,3′-oxindole], which takes place in a highly diastereoselective manner. Additional studies on mechanistic and preparative aspects of this reaction are underway and will be reported as results are forthcoming.

Acknowledgment. This work is dedicated to Professor Scott E. Denmark. We are grateful to Prof. Luc Angenot for his assistance in comparing the synthesized and natural products, Dr. B. Schweizer for X-ray analysis, and Prof. B. Jaun for NMR studies. Support has been provided by the ETH.

Supporting Information Available: Experimental procedures, spectral data, and structure correlation for all relevant compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) The synthesis of **12** commences with 1,4,5,6-tetrahydro-6-oxo-1-(phenylmethyl)-3-pyridinecarboxylic acid methyl ester, whose synthesis in two steps is reported: Cook, G. R.; Beholz, L. G.; Stille, R. G. *J. Org. Chem.* **1994**, *59*, 3575−3584. Reduction of the ester with $LiBH_4$ to the alcohol, deprotection of the benzyl moiety with Na in NH_3, protection of the hydroxyl-moiety with TBDPSCl, and protection of the amide with Boc_2O afforded **12**.
(9) Herdeis, C.; Hubmann, H. P. *Tetrahedron: Asymmetry* **1992**, *3*, 1213−1221.
(10) The facile conversion of the lactamol into the enamine was surprising, considering that other less substituted lactamols were converted into the corresponding enamine only upon heating to 160 °C in HMPA for several hours: Dieter, R. K.; Sharma, R. R. *J. Org. Chem.* **1996**, *61*, 4180−4184.
(11) The synthesis of **17** commences with 6-methoxyisatine which is commercially available, see Supporting Information.
(12) Particularly useful was an observed NOE between the aromatic C-9 proton and the appropriate H_β at C-14.
(13) For an in-depth discussion, see: Brown, R. T. In *Heterocyclic Compounds*; Saxon, J. E., Ed.; Wiley-Interscience: New York, 1983; Vol. 25, Part 4, pp 85−97.
(14) Compound **20** yielded suitable crystals for X-ray structure determination, thus confirming the stereochemical assignments made earlier on the basis of ^{1}H NMR, see Supporting Information.
(15) Burm, B. E. A.; Meijler, M. M.; Korver, J.; Wanner, J. M.; Koomen, G. *Tetrahedron* **1998**, *54*, 6135−6146.
(16) Although we did not anticipate stereoselectivity in this condensation reaction of the simple tryptamine derivative, it is important to note that stereoselective Pictet Spengler reactions have been documented employing tryptophan derivatives. Application of such methods at this stage would likely provide the desired product stereoselectively. (a) Watson, W. H.; Krawiec, M. J.; Cox, E. D.; Hamaker, L. K.; Li, J.; Yu, P.; Czerwinski, K. M.; Deng, L.; Bennet, D. W.; Cook, J. M. *J. Org. Chem.* **1997**, *62*, 44−61. (b) Waldmann, H.; Schmidt, G.; Jansen, M.; Geb, J. *Tetrahedron* **1994**, *50*, 11865−11884.

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