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New Route to the Ergoline Skeleton via Cyclization of 4-Unsubstituted Indoles

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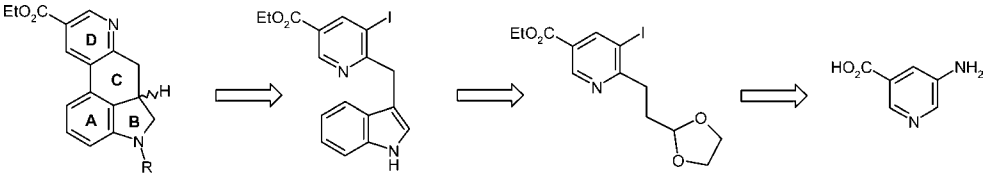
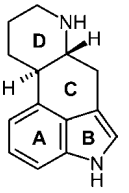
ABSTRACT



A new route to the ergoline skeleton has been developed that does not require prior functionalization of the indole 4-position. The indole nucleus is introduced late in the synthesis to allow for eventual efficient introduction of substituents in this region. Key steps include Negishi coupling of a three-carbon chain to a bromonicotinate ester, Fischer indole synthesis to facilitate incorporation of substituents via phenylhydrazines, and Pd-catalyzed cyclization to form the ergoline C ring.

Ergoline is a tetracyclic heterocycle (Figure 1) that forms the skeleton of a series of natural and semisynthetic compounds with a rich and well-studied pharmacology.[1] Ergolines exhibit a diversity of bioactivities including uterotonic, hypertensive, and antihypertensive activity; induction of hyperthermia and emesis; hallucinogenesis; neuroleptic activity; and control of the secretion of pituitary hormones.[2] Many have a potent influence on the neuroendocrine system via their interactions with monoamine neurotransmitter receptors. Others exhibit in vivo antitumor activity and tyrosine kinase inhibition.[3]

Although routes to ergolines are well represented in the literature,[4] they generally require preparation of a 4-substituted indole derivative at the outset.[5] These strategies are poorly suited for generation of derivatives for pharmacological exploration, particularly if diversity in the ergoline A ring is desired. The recent appearance in this journal of a report by Nichols[6] refuting the earlier published route to lysergic acid of Hendrickson[7] further illustrates the need for simpler, workable routes to these valuable compounds.



Ergoline

Figure 1. Rings A–D of the parent tetracycle ergoline.

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(1) Schardl, C. L.; Panaccione, D. G.; Tudzynski, P. *Alkaloids: Chem. Biol.* **2006**, *63*, 45–86.

(2) (a) Bovet, F. J. *The Story of Ergot*; Karger: Basel, 1970. (b) Berde, B., Schild, H. O., Eds. *Ergot Alkaloids and Related Compounds, Vol. 49, Handbook of Experimental Pharmacology*; Springer: Berlin, 1978. (c) Stadler, P. A.; Giger, R. K. *Natural Products and Drug Development*; Krogsgaard-Larsen, P., Christensen, C. H., Kofod, H. J., Eds.; Munksgaard: Copenhagen, 1984; p 463. (d) Eich, E.; Pertz, H. *Pharmazie* **1994**, *49*, 867–877.

(3) (a) Eich, E.; Eichberg, D.; Muller, W. E. *Biochem. Pharmacol.* **1984**, *33*, 523–526. (b) Eich, E.; Becker, C.; Sieben, R.; Maidhof, A.; Muller, W. E.; *J.*

(4) See, e.g., Liu's recent total synthesis of lysergic acid and references therein: Liu, Q.; Jia, Y. *Org. Lett.* **2011**, *13*, 4810–4813.

(5) Typically, 4-haloindoles or indole-4-boronic acids are required; e.g., the protected 4-iodotryptophan derivative required in ref 4.

(6) Bekkam, M.; Mo, H.; Nichols, D. E. *Org. Lett.* **2012**, *14*, 296–298.

(7) Hendrickson, J. B.; Wang, J. *Org. Lett.* **2004**, *6*, 3–5.

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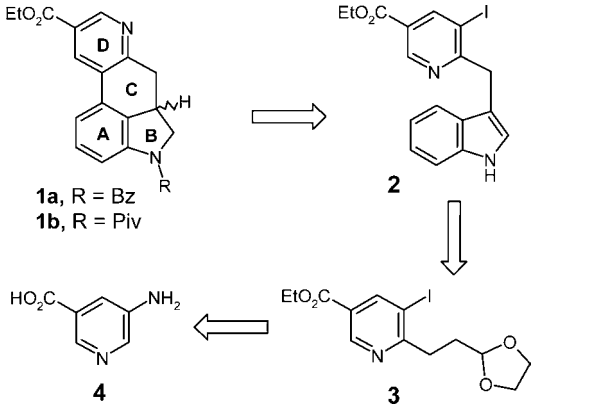
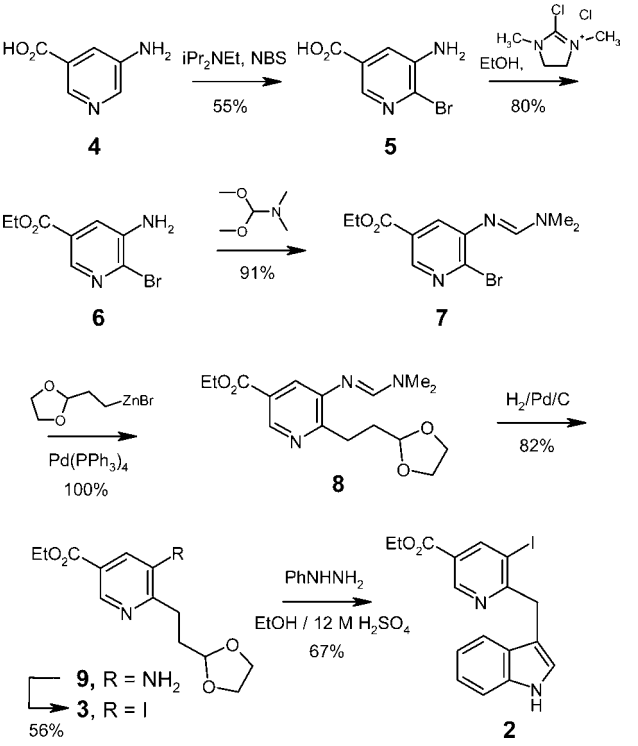
We therefore decided to pursue a route to the ergoline skeleton in which the key cyclization step would take place on a 4-unsubstituted indole (Scheme 1), greatly simplifying the preparation of precursors and allowing the A ring to be efficiently introduced late in the scheme. Interestingly, a similar cyclization strategy employing a Pschorr ring closure was attempted over half a century ago by Plieninger et al.,[8] although it resulted in the undesired irreversible oxidation of the newly formed C ring to a naphthalene derivative. We circumvented this difficulty with our choice of **1a** and **1b** as synthetic targets in which the indole 2,3-bond is reduced to the dihydro (indoline) derivative, preventing the potential migration of this bond to the C ring, a strategy first employed in Kornfeld's tour de force total synthesis of lysergic acid.[9]

Scheme 1. Retrosynthetic Analysis. Construction of the Indole Ring at a Late Stage Facilitates Introduction of Diversity in Ring A



Our first goal was to synthesize acetal **3** (Scheme 1), which would serve as the final common intermediate before introduction of diversity via the Fischer indole synthesis. We began with readily available 5-aminonicotinic acid **4**. The carboxylate salt formed from **4** and Hünig's base was smoothly brominated with NBS in methanol/acetonitrile to give reasonable yields of the crude 6-bromo derivative **5** (Scheme 2) as a finely divided dark brown precipitate upon reacidification with HCl. Although this crude material was practically insoluble in organic solvents other than DMF or DMSO and therefore difficult to purify, it was sufficiently pure to carry forward to the subsequent esterification step. Attempts to brominate **4** as a neutral (protonated) species resulted in complex mixtures, presumably because of the deactivating effect of the *p*-carboxylic acid substituent to electrophilic substitution at the desired 6-position. The electron-withdrawing nature of the carboxylic acid substituent is substantially eliminated upon deprotonation, as indicated by a marked difference in the Hammett substituent constant, σ, for the different protonation states ($\sigma = +0.45$ for *p*-CO_2H versus $\sigma = +0.0$ for *p*-CO_2^-).[10]

Scheme 2. Synthesis of Indole **2** via Final Common Intermediate **3**



DMC (2-chloro-1,3-dimethylimidazolinium chloride)[11] was chosen as a suitable activating agent for esterification of **5** (in ethanol, again as the DIPEA salt). The resulting ethyl ester **6** was easily purified by flash chromatography. A small amount of **6** was hydrolyzed with sodium hydroxide in methanol/water to give a clean sample of **5** as a light yellow crystalline solid suitable for characterization.

Since we required a mild nucleophile that would not attack the ester moiety of **6**, we chose the Negishi coupling[12] for addition of the three-carbon acetal side chain. We then required protection of the amino group as a nonprotic functionality. Heating amine **6** with DMF dimethyl acetal[13] gave an excellent yield of formamidine **7**,

(8) (a) Plieninger, H.; Schach von Wittenau, M.; Kiefer, B. *Ber*. **1958**, *91*, 1898–1905. (b) Plieninger, H.; Schach von Wittenau, M. *Ber*. **1958**, *91*, 1905–1909. (c) Plieninger, H.; Schach von Wittenau, M.; Kiefer, B. *Ber*. **1958**, *91*, 2095–2103.

(9) Kornfeld, E. C.; Fornefeld, E. J.; Kline, G. B.; Mann, M. J.; Morrison, D. E.; Jones, R. G.; Woodward, R. B. *J. Am. Chem. Soc*. **1956**, *78*, 3087–3114.

(10) McDaniel, D. H.; Brown, H. C. *J. Org. Chem*. **1958**, *23*, 420–427.

(11) Isobe, T.; Ishikawa, T. *J. Org. Chem*. **1999**, *64*, 6984–6988.

(12) Negishi, E. *Acc. Chem. Res*. **1982**, *15*, 340–348.

(13) Initially, we attempted to protect **6** by condensing it with benzaldehyde, but the resulting imine was sensitive to nucleophilic attack by the organozinc reagent during the subsequent Negishi coupling.

(14) Some examples of *o*-haloformamidines as substrates in palladium-catalyzed coupling reactions: (a) Dohle, W.; Staubitz, A.; Knochel, P. *Chem. Eur. J*. **2003**, *9*, 5323–5331. (b) Hikishima, S.; Minakawa, N.; Kuramoto, K.; Fujisawa, Y.; Ogawa, M.; Matsuda, A. *Angew. Chem., Int. Ed*. **2005**, *44*, 596–598. (c) Chuaqui, C.; Cossrow, J.; Dowling, J.; Guan, B.; Hoemann, M.; Ishchenko, A.; Jones, J. H.; Kabigting, L.; Kumaravel, G.; Peng, H.; Powell, N.; Raimundo, B.; Tanaka, H.; Van Vloten, K.; Vessels, J.; Xin, Z. PCT Int. Appl. WO 2010078408, 08 Jul 2010.

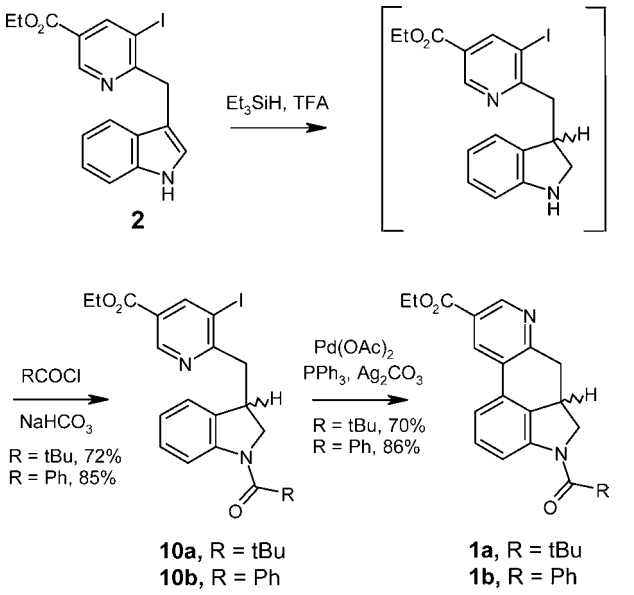
and the subsequent Negishi coupling proceeded in quantitative yield to give acetal **8**. Based on similar reactions we have conducted on other substrates, it appears that the formamidine moiety accelerates the coupling reaction by a chelation effect.[14] The required organozinc reagent, 2-[(1,3-dioxolanyl)ethyl]zinc bromide, is commercially available.

The formamidine protecting group of **8** was most conveniently removed by catalytic hydrogenation[15] in ethanol to give amine **9** cleanly. Diazotization of **9** and displacement with iodide proceeds in moderate yields due to the necessity of using acids and/or electrophiles in the presence of the sensitive acetal side chain. We initially attempted the transformation under the anhydrous conditions of Hartley et al.[16] but obtained only a ~35% yield of iodopyridine **3**; a better yield (56%) was eventually obtained by simply using classical diazotization conditions (potassium nitrite/aqueous HCl).

Iodopyridine **3** is the key final common intermediate, allowing for the introduction of diversity by the choice of substituted phenylhydrazines as reaction partners in the Fischer indole synthesis, although in the present work we utilize only the parent phenylhydrazine itself. The Fischer synthesis is conducted in ethanol/H_2O/H_2SO_4, and several trials were required in order to find a combination of water concentration and acidity that would allow for selective hydrolysis of the acetal moiety in the presence of an ethyl ester. In the end, ~4 equiv of H_2SO_4 as a 12 M aqueous solution added to the ethanolic reaction mixture appeared to be optimal, and indole **2** was obtained in acceptable yield.

Finding the proper strategy for cyclization of **2** or one of its derivatives onto the unsubstituted indole 4-position to create the ergoline C ring also required a bit of investigation. The palladium-assisted cyclization conditions optimized by Harayama[17] during the synthesis of a benzo[*c*]phenanthridine alkaloid (and later employed by Li et al.[18] for cyclization of an iodobenzene derivative to a dihydrophenanthridine) appeared promising but were unsuccessful when applied to the *N*-pivaloyl derivative of **2**. (The pivaloyl protecting group had previously been employed by Goto[19] and then Moldvai[20] as a way to direct intramolecular acylation of indole-3-propionic acid to the indole 4-position in preference to the 2-position, and we had hoped that it might also be successful in directing the intramolecular Pd-catalyzed cyclization in similar fashion.) Therefore, we decided to eliminate all possibility of reactivity at the indole 2-position by first reducing the indole 2,3-bond and then acylating

Scheme 3. Reduction, Indoline Protection, and Cyclization



with pivaloyl chloride using classical two-phase Schotten–Baumann conditions to give protected indoline **10a** (Scheme 3). Upon subjecting **10a** to the cyclization conditions in the presence of silver carbonate, we were thrilled to observe a successful clean cyclization to give the target tetracycle **1a**.

In similar fashion, acylation with benzoyl chloride gave **10b**, and cyclization under identical conditions gave **1b**. The yield of **1b** was somewhat higher than that of **1a**. Electron-rich acyl substituents on the indoline N(1) position may deactivate the system to cyclization as compared to electron-poor substituents; this speculation is further supported by our observation that *N*-Boc protection leads to even lower cyclization yields.

Efforts are underway to reduce the D ring and reoxidize the B ring of **1a** and/or **1b** to achieve the formal synthesis of naturally occurring ergolines; we will report these developments in a future publication.

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Supporting Information Available. Experimental procedures and spectral data (^{1}H and ^{13}C NMR) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(17) Harayama, T.; Akiyama, T.; Kawano, K. *Chem. Pharm. Bull.* **1996**, *44*, 1634–1636.
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