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A New Synthesis of Lysergic Acid

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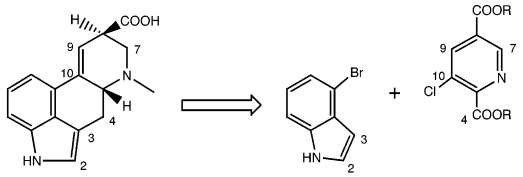
ABSTRACT



1 Lysergic Acid

(±)-Lysergic acid (1) has been synthesized via an economical 8-step route from 4-bromoindole and isocinchomeronic acid without the need to protect the indole during the synthesis. Initial efforts to form the simpler 3-acylindole derivatives first and then cyclize these were unsuccessful in the cyclization step.

The ergot alkaloids pose an unusual opportunity for synthesis. The central alkaloids are all amides of lysergic acid (**1**) and all possess a broad range of pharmacological activity.[1−3] Only one of these, the diethylamide (LSD), however, is strongly and notoriously psychoactive. As such it is listed as a class I controlled substance. Since both the natural and synthetic derivatives are easily convertible to lysergic acid and so to its diethylamide, all of these are also controlled substances. As a result this potential pharmacological treasure is essentially unavailable for practical clinical testing.

We considered that a derivative of lysergic acid bearing an unremoveable substituent, like an added C-alkyl group, could not be converted to lysergic acid itself or its amide. Such derivatives would probably retain the broad pharmacological activity of the ergot family but might easily avoid the unique hallucinogenic property of LSD. This idea encouraged us to seek a short, practical synthesis route to lysergic acid suitable for incorporation of C-alkyl starting materials to create these derivatives.

Lysergic acid has already been synthesized about eight times.[4] The shortest path has 11 steps and none are serious candidates for practical manufacture. Every synthesis to date contains redundant protection/deprotection sequences, often as indole starting materials reduced and acylated, only at the end reconstituted to the indole form. To eliminate this redundancy we decided that the indole should be carried through intact.

The simplest convergent bondset for assembling the lysergic skeleton should be the boldface bonds in ring C, which just arise from indole and nicotinic acid starting materials. No previous syntheses had utilized this approach except the Julia route, which did not carry the indole moiety through unchanged.

Of the two initial constructions necessary for the bondset in Figure 1 we began with the simplest (bond **b**) via an

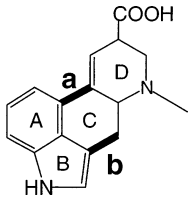


Figure 1. Bondset of lysergic acid synthesis.

acylation of indole or 4-haloindoles[5] **2** with the acid chloride **3** from the commercially available 6-carboxynicotinic acid (isocinchomeronic acid), as outlined in Scheme 1. The acid

(1) Hofmann, A. *Ergot Alkaloids, Pharmacology*; Spano, P. F., Trabucchi, M., Eds.; Karger: Basel, Switzerland, 1978; Vol. 16, Supp. 1, p 1.
(2) Lemberger, L. *Fed. Proc.* **1978**, *37*, 2176.
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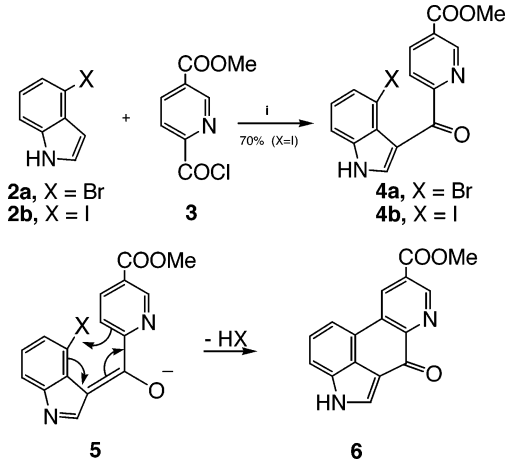
Scheme 1. Attempt via Bondset **ba** Approach[a]



[a] Reagents: (i) $EMgBr/ZnCl_2/Et_2O$.

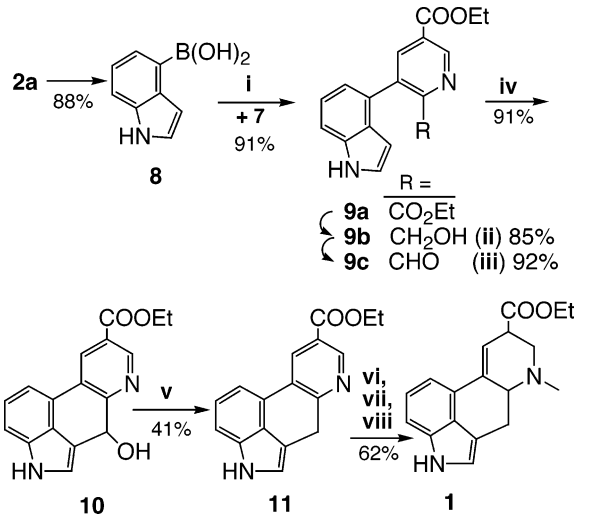
was esterified, selectively hydrolyzed only at the 6-position[6] with aqueous $Cu(NO_3)_2$, and converted ($SOCl_2$) to **3**. The Grignard reagents from **2** were acylated with **3** to form **4**. However, a number of attempts at palladium-catalyzed cyclizations of **4** (X = Br or I) or reduced pyridine derivatives of **4** and their *N*-methyl salts were all unsuccessful.

We also considered that a thermal pericyclic cyclization of the anion **5** of **4** might be accessible with subsequent loss of HX to form **6**, but several trials of this at elevated temperatures, with or without added base, led only to intractable tars.

The alternative path to close ring C, making bond **a** first, was ultimately successful, as summarized in Scheme 2. For this approach we needed a nicotinic acid derivative with a halogen marking the 5-position.

The common introduction of halogen on pyridines, via $SOCl_2$ on the *N*-oxide,[7] provides only the ortho/para halides. However, sulfonyl halides can give rise to meta substitution[8] and the reaction of the *N*-oxide of 6-carboxynicotinic acid with thionyl chloride affords[9] the *m*-chloro derivative **7** on workup with methanol. We believe this results from first

Scheme 2. Synthesis of Lysergic Acid via Bondset **ab** Approach[a]



[a] Reagents: (i) $Pd(PPh_3)_4/Na_2CO_3$(aq)/EtOH; (ii) $NaBH_4/CaCl_2$/EtOH; (iii) $MnO_2/CHCl_3$; (iv) NaOH/MeOH; (v) $NaBH_4$/TFA/CH_2Cl_2; (vi) MeI/CH_2Cl_2; (vii) $NaBH_4$/MeOH; (viii) NaOH /EtOH.

forming the normal, nonplanar *p*-chloro intermediate in Figure 2, which can then collapse via the pericyclic rearrangement shown and subsequent loss of the *p*-chloride to afford **7**.

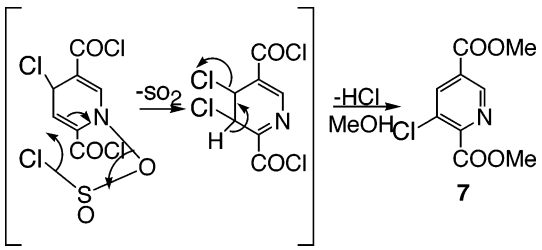


Figure 2. Proposed mechanism for formation of **7**.

When the 4-haloindoles **2** were converted to the boronic acid **8** (via KH + BuLi and $B(OBu)_3$), the Suzuki coupling was successful in forming **9a** in 91% yield. While this work was in progress, a closely related reaction appeared in a note by Doll[10] coupling **8** with 5-bromonicotinic ester, but the subsequent addition of the missing carbon 4 for lysergic acid failed.

We presumed that an appropriate base would easily initiate the cyclization of the diester **9a** to the tetracyclic ketone corresponding to **10**. However, treatment of the diester with NaH, even in glycol at 197 °C, yielded only starting material. A number of attempts to cyclize the corresponding, very

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(5) Somei, M.; Kizu, K. *Chem. Pharm. Bull.* **1985**, *33*, 3696.

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(8) Katritzky, A. R.; Lagowski, J. M. *The Chemistry of the Pyridine N-Oxides*; Academic Press: New York, 1971; p 288.

(9) Quarroz, D. Swiss Patent CH 657,124, 1986; *Chem. Abstr.* **1987**, *106*, 32852.

(10) Doll, M. K.-H. *J. Org. Chem.* **1999**, *64*, 1372.

insoluble diacid with thionyl chloride or variants of PPA led only to recovery of diacid or intractable mixtures with no evidence of cyclization.

Following a similar but intermolecular version from Potier[11] we reduced the ester selectively[12] with $NaBH_4$ and $CaCl_2$ to **9b** and then oxidized it to the aldehyde **9c** with MnO_2. The aldehyde cyclized at room temperature easily and quantitatively with only 2 mol % of NaOH to yield **10**. Various efforts to cyclize the alcohol **9b** or its tosylate to **11** all recovered only starting materials. The difference in the ease of cyclization of **9c** over its precursors surprised us but we became convinced from models that there was severe steric resistance to the stereoelectronic demands for cyclization except for the aldehyde case.

Typical reduction[13] of the indole-alcohol **10** with $NaBH_4$/TFA afforded **11**, which proved to be unstable, decomposing in a matter of hours. Accordingly, the remaining steps were carried through without isolation. Freshly prepared **11** was methylated directly with methyl iodide and the crude salt **12** reduced with excess $NaBH_4$ in methanol to a mixture of methyl lysergate and its cis-isomer isolysergate in a 6:1 ratio, as a pale yellow solid.

These diastereomers are reported to be somewhat unstable[14] and so were immediately hydrolyzed to lysergic acid with NaOH, which also equilibrated them to the more stable lysergic acid, which was then finally recrystallized to mp 241−242 °C (lit. 242−243 °C).

(11) Potier, P.; Langlois, Y. *Tetrahedron* **1975**, *31*, 419.
(12) Matsumoto, I.; Yoshizawa, J. Japanese Patent JP 48029783, 1973.
(13) Gribble, G. W.; Nutaitis, C. F. *Org. Prep. Proced. Int.* **1985**, *17*, 317.
(14) (a) Glenn, A. L. *Quart. Rev.* **1954**, *8*, 192. (b) Stoll, A.; Petrzilka, T. *Helv. Chim. Acta* **1953**, *36*, 1125.

The ^1H NMR spectra of the mixed esters were identical with spectra kindly provided by Prof. Ichiya Ninomiya, and the NMR spectra (^1H and ^{13}C) of the lysergic acid agreed with that of a natural sample kindly provided by Dr. David Nichols.

The last three operations (**10** to **1**) are carried out easily in good yield without isolation and purification; this result lends value to the initial conception in Figure 1 that the most economical synthesis of lysergic acid is one that originates in the two main starting materials, a simple indole and a nicotinic acid derivative, both retaining their aromaticity to the very end. This synthesis comprises eight steps from isocinchomeronic acid and 4-bromoindole and proceeds in an unoptimized overall yield of 10.6%. Chirality is only introduced in the final reduction step, and enantioselective measures for this reduction have not yet been examined, nor has the parallel synthesis of C-alkyl derivatives.

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Supporting Information Available: Experimental details and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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