Tetrahedron Letters,Vol.27,No.30,pp 3469-3470,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

WITTIG METHYLENATION OF 9,10-DIDEHYDRO-6-METHYLERGOLIN-8-ONE, A NOVEL SYNTHESIS OF LYSERGENE AND ITS SUBSEQUENT CONVERSION TO AGROCLAVINE

William J. Wheeler

Lilly Research Laboratories, Eli Lilly and Co., Indianapolis, IN 46285, USA

Summary: N-p-Ts-lysergene (6) was synthesized by the reaction of N-p-Ts-9,10-didehydro-6-methylergolin-8-one (5) with methylene triphenylphosphorane. Subsequent lithium/ammonia reduction of 6 yielded agroclavine (3).

As part of an ongoing research project, we wished to prepare 17-[^{14}C]-agroclavine. A total synthesis would be difficult, since it was necessary to maintain both relative and absolute stereochemistry in the final product. We felt that it was feasible to insert the label in an intermediate derived from lysergic acid (1) and convert it to the desired product while maintaining control of the stereochemistry.

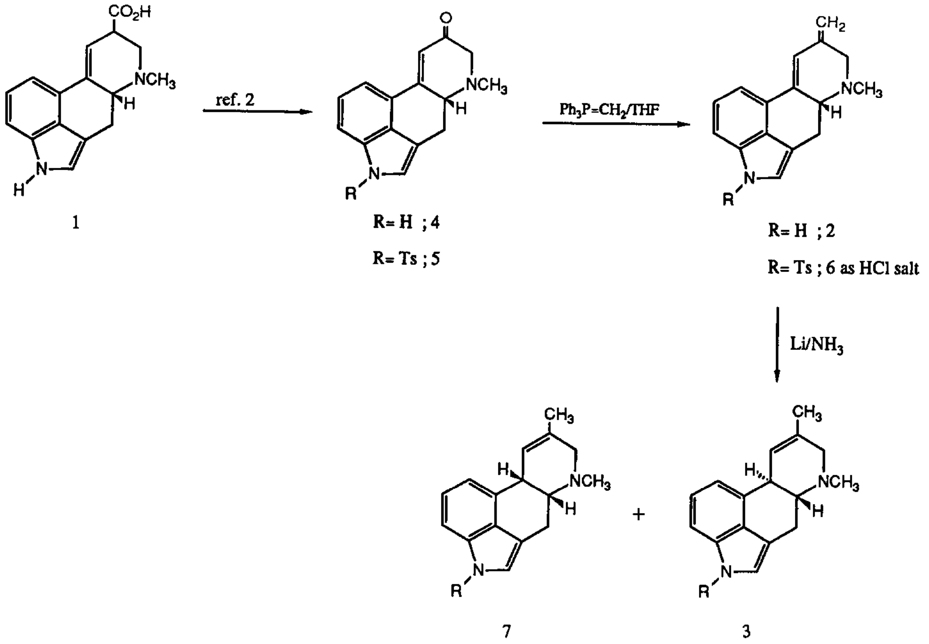
Ninomiya recently reported the first total synthesis of ±-lysergene (2) and ±-agroclavine (3) in which 2,3-dihydrolysergene was converted to 2,3-dihydro-agroclavine (as well as its 10-epi-derivative) by reduction with sodium/liquid ammonia as the penultimate step.[1] Since 9,10-didehydro-6-methylergolin-8-one (4) has been synthesized from lysergic acid (1) via a five step sequence which maintains absolute stereochemistry[2], we envisioned the synthesis of lysergene from 4 via a Wittig reaction.

Reaction of 4[2,3] with methylene triphenylphosphorane (derived from methyltriphenylphosphonium iodide/potassium t-butoxide) yielded lysergene (2) although in only 10-15% yield. Deprotonation of the indole nitrogen serves to deactivate the ketone significantly to further reaction, presumably because of the extended conjugation of the indole ring to the ketone. The carbonyl stretching frequency of the ketone in 4 appears at 1664 cm^{-1}, somewhat lower than that of normal α,β-unsaturated ketones.

Protection of the indole nitrogen in 4 with the N-tosyl group allowed the Wittig reaction to proceed in much higher yield. Reaction of 4 with p-toluene-sulfonyl chloride/potassium carbonate was erratic; however, utilization of cesium carbonate resulted in the clean conversion of 4 to 5 in moderate yield. Subsequent reaction of 5 with methylene triphenylphosphorane (3 equivalents) in THF at -78°/24 hours produced N-Ts-lysergene as its HCl salt (6) in 47% yield (based on 5).

Reduction of 6 with Li/ammonia yielded agroclavine (3) in 52% yield after chromatography. To our surprise only a trace of 10-*epi*-agroclavine (7) was present in the crude reaction mixture. Under the same conditions reduction of lysergene (2) yielded (3) and (7) in approximately a 2:1 ratio. These latter results are similar to those reported by Ninomiya[1] for the reduction of 2,3-dihydrolysergene. We are currently investigating the mechanism of this stereoselective reduction of 6.

The synthesis of lysergene (2) and 6 via the Wittig reaction should be useful in the synthesis of other interesting ergoline compounds. This work represents a new formal total synthesis of ±-agroclavine (3) since the starting ketone (4) has been synthesized from indole-3-propionic acid as described by Kornfeld *et al.*,[4] and Bach *et al.*[3] The synthesis of 17-[^{14}C]-agroclavine and its analogues utilizing these procedures will be the subject of a forthcoming full paper to be published elsewhere.[5]



References:

1. T. Kiguchi, C. Hashimoto, and I. Ninomiya, Heterocycles, 1984, 22, 43.
2. L. Bernardi, E. Gandini, and A. Teperilli, Tetrahedron, 1974, 30, 3447.
3. N. J. Bach, D. A. Hall, and E. C. Kornfeld, J. Med. Chem., 1974, 17, 312.
4. E. C. Kornfeld, E. J. Fornefeld, B. G. Kline, M. J. Mann, D. E. Morrison, R. G. Jones, and R. B. Woodward, J. Amer. Chem. Soc., 1956, 78, 3087.
5. All compounds were characterized by IR and NMR spectroscopy. For new compounds, adequate analytical and/or mass spectroscopic data have been obtained.

(Received in USA 18 April 1986)