

## A NEW SYNTHESIS OF (+)-LYSERGIC ACID

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Abstract ——— Reductive photocyclization of the enamide (2) followed by the ring opening of the resulting dihydrofuran derivative (4) completed a new total synthesis of (+)-lysergic acid.

Among many of the synthetic challenges to lysergic acid, a representative ergot alkaloid, only four groups<sup>1</sup> have reached to the final goal of total synthesis of this particular alkaloid. In connection with our synthetic studies<sup>2</sup> on ergot alkaloids, we now report a new formal total synthesis of (+)-lysergic acid by the route that we have just developed on the benzo(f)quinoline derivatives.<sup>3</sup>

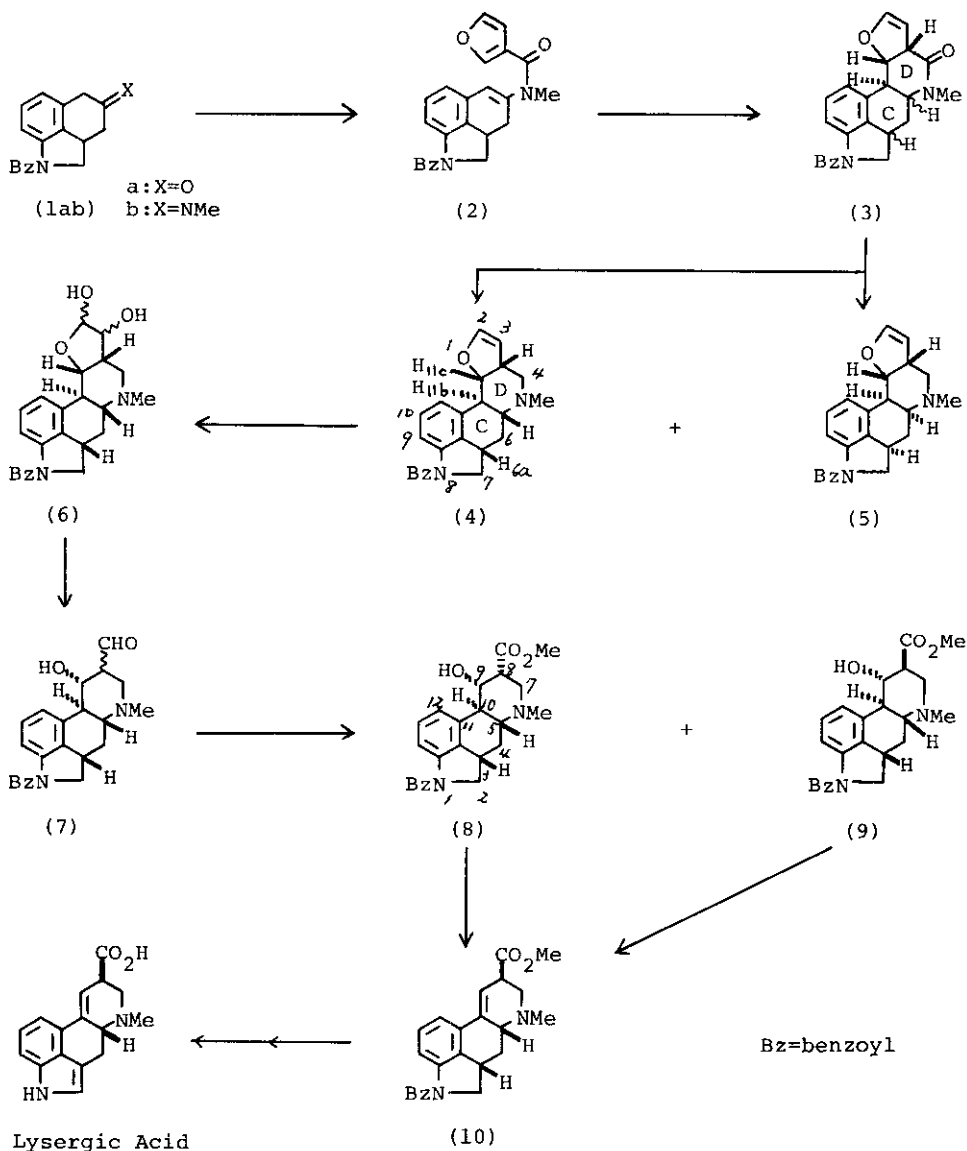
The known tricyclic ketone (1a)<sup>1a,4</sup> was treated with methylamine to give the unstable imine (1b) which was readily converted into the enamide (2), m.p. 130-131° C,  $\nu$ , 1640-1620  $\text{cm}^{-1}$ , in 96 % yield upon acylation with 3-furoyl chloride in the presence of triethylamine. Reductive photocyclization<sup>5</sup> of the enamide (2) in the presence of sodium borohydride in a benzene-methanol (10 : 1) solution at 4-5° C afforded the hydrogenated lactam (3),  $\nu$ , 1655 and 1645  $\text{cm}^{-1}$ , in 81 % yield as a mixture of two stereoisomers with respect to the C/D-ring juncture. Reduction of the above lactam (3) with lithium aluminum hydride followed by rebenzoylation with benzoyl chloride yielded a mixture of two N-benzoates (4 and 5), of which the desired C/D-trans-amine (4) was readily separated by crystallization with ether in 61 % yield while the C/D-cis-amine (5) was isolated by column chromatography of the above mother liquor in 9 % yield. The major trans-amine (4) was obtained as colorless needles from benzene-ether, m.p. 187-189° C, and exhibited  $\nu$ , 1640  $\text{cm}^{-1}$ , and  $^1\text{H}$  nmr,  $\delta$  6.47 (br s, 2-H), 4.98 (br s, 3-H), 4.68 (t, J=10Hz, 11c-H), 3.14 (t, J=10Hz, 11b-H), 2.46 (s, NMe), 2.22 (td, J=10 and 2Hz, 5a-H), and 1.43 (q, J=10Hz, 6ax-H), and the minor cis-amine (5) was obtained also as colorless needles from

benzene, m.p. 172-174° C, and exhibited ir, 1640  $\text{cm}^{-1}$ , and  $^1\text{H}$  nmr,  $\delta$  6.43 (br s, 2-H), 4.94 (br s, 3-H), 4.46 (t,  $J=10\text{Hz}$ , 11c-H), 3.42-3.22 (m, 11b-H), 2.50 (s, NMe), 2.22 (br d,  $J=11\text{Hz}$ , 5a-H), and 1.44 (q,  $J=11\text{Hz}$ , 6ax-H). The stereochemistry of these amines (4) and (5) was deduced from analysis of their nmr spectra upon comparisons with those<sup>3</sup> of the previously prepared compounds having identical partial structures with (4) and (5), in addition to the well-documented facts<sup>1c,6</sup> on the relative configuration of 6a-H in the ergoline series of compounds. Furthermore, the mechanistic consideration<sup>5</sup> of enamide photocyclization suggests the trans-configuration between two hydrogens at the ring junctures of 11b and 11c.

Oxidation of the trans-amine (4) with osmium tetroxide followed by treatment with hydrogen sulfide afforded the glycol (6) in 53 % yield, which was found to be a mixture of two cis-glycols in the ratio of three to two in favor of the  $\beta$ -glycol from the nmr spectra. Without separation, cleavage of the glycol (6) with sodium metaperiodate in methanol-water (1 : 1) gave an unstable mixture of epimeric hydroxy-aldehydes (7), which were dissolved in methanol-acetone and treated with chromic trioxide in sulfuric acid at 0° C for 1 hr to give a pair of the hydroxy-esters (8 and 9), epimeric with respect to relative configuration of the ester group at C<sub>8</sub>, which were separated by preparative t.l.c. The compound (8) was obtained in 11 % yield as a viscous oil and exhibited ir, 1710 and 1630  $\text{cm}^{-1}$ , and  $^1\text{H}$  nmr,  $\delta$  7.90 (br d,  $J=8\text{Hz}$ , 12-H), 3.86 (br dd,  $J=11$  and  $4\text{Hz}$ , 9-H), 3.80 (s, COOMe), 3.48 (dd,  $J=12$  and  $3\text{Hz}$ , 7eq-H), 3.17 (t,  $J=10\text{Hz}$ , 10-H), 3.01 (m, 8-H), 2.47 (dd,  $J=12$  and  $3\text{Hz}$ , 7ax-H), 2.35 (s, NMe), and 1.41 (q,  $J=12\text{Hz}$ , 4ax-H), thus suggesting its axially oriented ester group. The compound (9) was obtained in 14 % yield as colorless needles from methanol, m.p. 224-226° C, and exhibited ir, 1720 and 1630  $\text{cm}^{-1}$ , and  $^1\text{H}$  nmr,  $\delta$  7.83 (br d,  $J=8\text{Hz}$ , 12-H), 4.04 (t,  $J=10\text{Hz}$ , 9-H), 3.78 (s, COOMe), 3.27 (dd,  $J=12$  and  $5\text{Hz}$ , 7eq-H), 2.98 (ddd,  $J=12$ , 10, and  $5\text{Hz}$ , 8-H), 2.80 (t,  $J=10\text{Hz}$ , 10-H), 2.57 (t,  $J=12\text{Hz}$ , 7ax-H), 2.42 (s, NMe), and 1.47 (q,  $J=12\text{Hz}$ , 4ax-H), therefore showing the equatorial orientation of ester group. Dehydration of both the hydroxy-esters (8) and (9) was performed by warming with phosphorus oxychloride-phosphoric acid in pyridine at 40° C to afford identical unsaturated ester (10) in the yields of 29 % from (8) and 28 % from (9) respectively. Contrary to the case of the model compounds<sup>3</sup> which gave a mixture of epimeric unsaturated esters upon dehydration, this result of obtaining a single unsaturated ester (10) is consistent with the facts that the  $\beta$ -equatorial esters

including (10) are thermodynamically more stable than the corresponding  $\delta$ -axial esters in the cases of lysergic acid derivatives.<sup>1c,7</sup>

This unsaturated ester (10) was found to be identical in all respects with the authentic compound prepared in the course of the syntheses of (+)-lysergic acid by Ramage<sup>1c</sup> and also by Woodward<sup>1a</sup> upon comparisons with their spectral evidences.



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\* Melting points are uncorrected. IR spectra were measured in chloroform solutions and nmr spectra were recorded on a Varian XL-200 at 200MHz in deuteriochloroform solutions with TMS as internal standard.

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