HETEROCYCLES, Vol 19, No 12, 1982

A NEW SYNTHESIS OF (±)-LYSERGIC ACID

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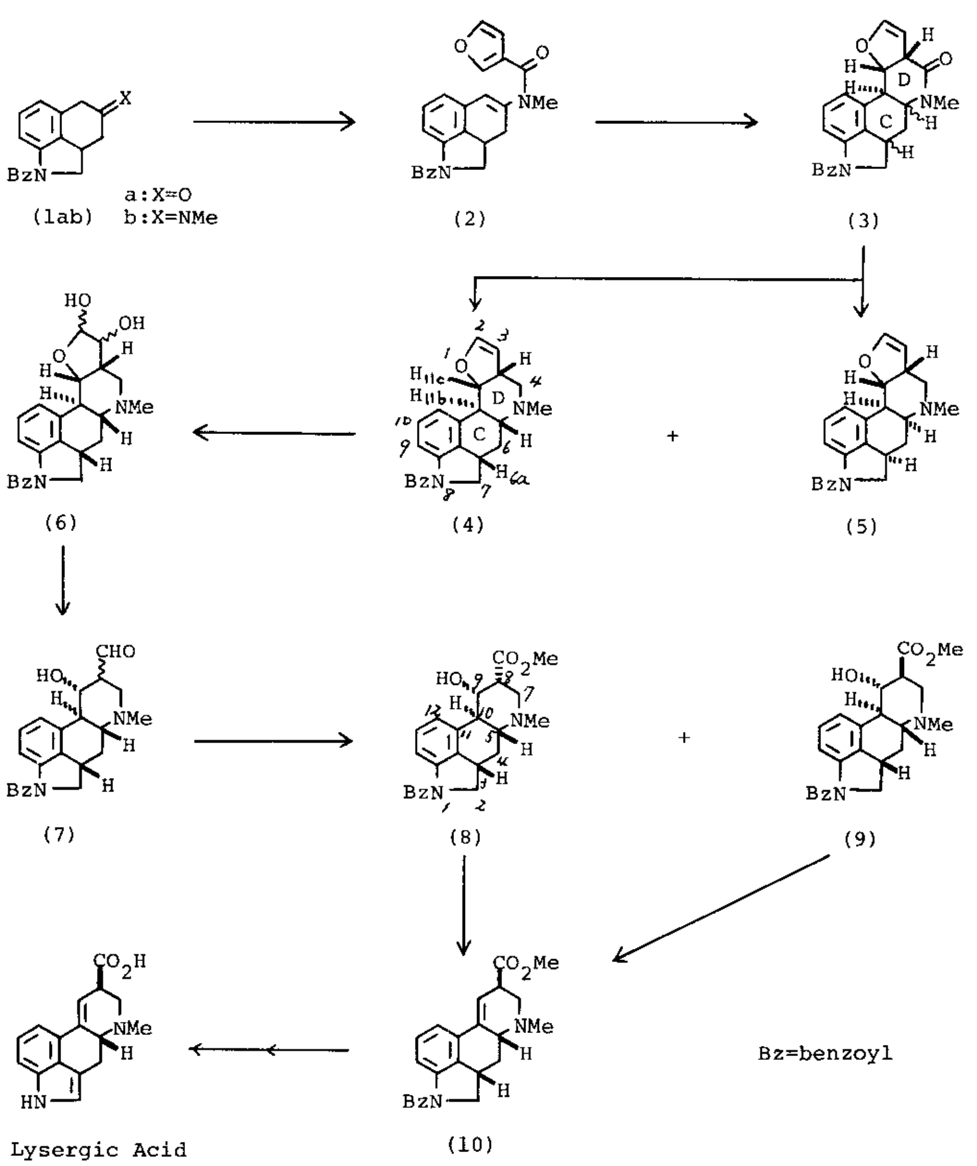
Abstract ——— Reductive photocyclization of the enamide (2) followed by the ring opening of the resulting dihydrofuran derivative (4) completed a new total synthesis of (±)-lysergic acid.

Among many of the synthetic challenges to lysergic acid, a representative ergot alkaloid, only four groups[1] have reached to the final goal of total synthesis of this particular alkaloid. In connection with our synthetic studies[2] 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.[3]

The known tricyclic ketone (1a)[1a,4] was treated with methylamine to give the unstable imine (1b) which was readily converted into the enamide (2), m.p. 130-131° C, ir, 1640-1620 cm^{-1}, in 96 % yield upon acylation with 3-furoyl chloride in the presence of triethylamine. Reductive photocyclization[5] 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), ir, 1655 and 1645 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 ir, 1640 cm^{-1}, and ^1H nmr, δ 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 cm^{-1}, and ^1H nmr, δ 6.43 (br s, 2-H), 4.94 (br s, 3-H), 4.46 (t, J=10Hz, 11c-H), 3.42-3.22 (m, 11b-H), 2.50 (s, NMe), 2.22 (br d, J=11Hz, 5a-H), and 1.44 (q, J=11Hz, 6ax-H). The stereochemistry of these amines (4) and (5) was deduced from analysis of their nmr spectra upon comparisons with those[3] of the previously prepared compounds having identical partial structures with (4) and (5), in addition to the well-documented facts[1c,6] on the relative configuration of 6a-H in the ergoline series of compounds. Furthermore, the mechanistic consideration[5] 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 β-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_8, 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 cm^{-1}, and ^1H nmr, δ 7.90 (br d, J=8Hz, 12-H), 3.86 (br dd, J=11 and 4Hz, 9-H), 3.80 (s, COOMe), 3.48 (dd, J=12 and 3Hz, 7eq-H), 3.17 (t, J=10Hz, 10-H), 3.01 (m, 8-H), 2.47 (dd, J=12 and 3Hz, 7ax-H), 2.35 (s, NMe), and 1.41 (q, J=12Hz, 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 cm^{-1}, and ^1H nmr, δ 7.83 (br d, J=8Hz, 12-H), 4.04 (t, J=10Hz, 9-H), 3.78 (s, COOMe), 3.27 (dd, J=12 and 5Hz, 7eq-H), 2.98 (ddd, J=12, 10, and 5Hz, 8-H), 2.80 (t, J=10Hz, 10-H), 2.57 (t, J=12Hz, 7ax-H), 2.42 (s, NMe), and 1.47 (q, J=12Hz, 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[3] 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 β-equatorial esters including (10) are thermodynamically more stable than the corresponding α-axial esters in the cases of lysergic acid derivatives.[1c,7]

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[1c] and also by woodward[1a] upon comparisons with their spectral evidences.



ACKNOWLEDGEMENT

This work was supported by grants to I.N. and T.K. from the Ministry of Education, Science, and Culture (Japan). We warmly thank Professor R. Ramage, The University of Manchester, for his generous gifts of spectra of the authentic samples and his encouragement.

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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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Received, 14th August, 1982