Communications to the Editor

[Chem. Pharm. Bull.
34(1) 442—443 (1986)]

A NEW SYNTHESIS OF (±)-LYSERGIC ACID

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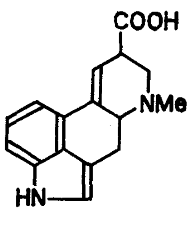
A new and simple synthesis of (±)-lysergic acid from the aldehyde (5) is described involving aldol condensation with 3 in the presence of LDA as a key reaction.

KEYWORDS —— lysergic acid; total synthesis; aldol condensation; mesylation; 1,8-diazabicyclo[5.4.0]-7-undecene

Several methods for the synthesis of lysergic acid have been explored[1a-1e] since the first success by Woodward in 1956.[2] Among these, our attention was focused on the Ramage method[1b] which is based on a mechanism involving the racemization of lysergic acid and isolysergic acid. Here we describe a new and simple synthesis of (±)-lysergic acid by a modified Ramage method using tetrahydroindeno[2,1-*b*]pyridine derivatives.[3]

The ketone (1)[2] was converted to the acid chloride (2) *via* the six-step route described previously.[4] Preparation of the anion of 3 (LDA/THF/-78°C) and its reaction with 2 did not lead to the desired formation of β-keto ester (4) contrary to the model experiment.[4] However the aldol condensation of the anion of 3 with the aldehyde (5),[2] prepared by hydrogenolysis of 2 [10% Pd-$BaSO_4$/H_2/N,N-dimethylaniline/toluene-EtOAc(1:1)/70-80°C], afforded the alcohol (6) in 99% yield as a diastereoisomeric mixture.[5] This was converted (MsCl/Et_3N/CH_2Cl_2) into the mesylate (7). Without purification this substance was subjected to the de-*tert*-butoxycarbonylation sequence (dry HCl gas/EtOAc/r.t.), then treated with DBU in DMSO at room temperature. The resulting reaction mixture was purified by column chromatography (silica gel/benzene:EtOAc=1:1) to give a mixture of 8/9 (2:1 by ^{1}H-NMR) in 42.4% overall yield from 6 and 11[6] in 6.8% overall yield from 6, mp 178-180°C (from EtOAc); IR (KBr) 1710, 1645 cm^{-1}; UV (C_2H_5OH) 267 (4.09), 293 nm (3.95); ^{1}H-NMR ($CDCl_3$) δ 1.30 (3H, t, *J*=7.3 Hz), 1.54 (1H, td, *J*=13 and 3 Hz), 2.46 (3H, s), 2.82 (1H, q, *J*=3.6 Hz), 2.98 (1H, dt, *J*=16.2 and 3 Hz), 4.22 (2H, m), 4.50 (1H, br s), and 6.8-



Lysergic Acid

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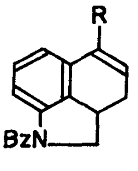
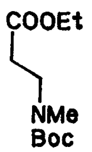


2 : R=COCl
5 : R=CHO



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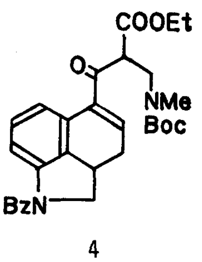

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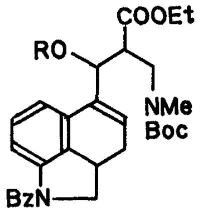
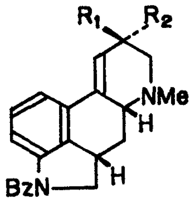
Bz=Benzoyl, Boc=*tert*-Butoxycarbonyl

7.6 (9H, m). Recrystallization of a mixture of 8/9 from EtOAc gave 8, mp 147-148°C; IR (KBr) 1730, 1640 cm^{-1}; UV (C_2H_5OH) 254 (4.51), 307 nm (3.80); ^{1}H-NMR(CDCl$_3$) δ 1.31 (3H, t, *J*=7.3 Hz), 1.39 (1H, q, *J*=11.5 Hz), 2.50 (3H, s), 2.67 (1H, t, *J*=11.5 Hz), 3.04 (1H, br d, *J*=11.5 Hz), 3.26 (1H, dd, *J*=11.5 and 6.1 Hz), 3.41 (1H, m), 3.62 (1H, m), 3.70 (1H, t, *J*=11 Hz), 4.22 (2H, q, *J*=7.3 Hz), 6.55 (1H, s), and 7.26-7.60 (8H, m). Hydrolysis (MeOH/conc. HCl/reflux) of 8 and esterification (MeOH/dry HCl gas/r.t.) followed by mild benzoylation (BzCl/MeOH) afforded 10, mp 165-168°C, whose IR and ^{1}H-NMR spectra are identical with those of the authentic sample prepared in the course of the synthesis of (±)-lysergic acid by Ninomiya.$^{7)}$

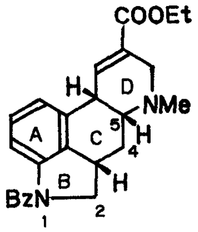
Thus, we have succeeded in developing a simple synthesis in few steps of (±)-lysergic acid in good overall yield.



6 : R=H
7 : R=SO_2Me



8 : R_1=COOEt, R_2=H
9 : R_1=H, R_2=COOEt
10 : R_1=COOMe, R_2=H



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ACKNOWLEDGEMENT We are grateful to Professor I. Ninomiya, Kobe Women's College of Pharmacy, for a gift of spectra of the authentic sample and his warm encouragement.

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3) R. Yoneda, T. Terada, S. Satoda, and T. Kurihara, *Heterocycles*, 23, 2243 (1985).

4) R. Yoneda, T. Terada, S. Harusawa, and T. Kurihara, *Heterocycles*, 23, 557 (1985).

5) This was found to be a mixture of two components in the ratio of 1:1. They were separated by column chromatography (silica gel/benzene:EtOAc=3:1), but their stereochemistries have not been determined at this stage.

6) Ramage$^{1b)}$ reported that the corresponding methyl ester of 11 could not be isolated in pure form due to contamination with 10. The ^{1}H-NMR signal of 5-H of 11 appeared as a quartet with coupling constants of 3.6 Hz, thus suggesting the C/D-*cis* ring junction.

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(Received November 20, 1985)