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A NEW SYNTHESIS OF ($\pm$)-LYSERGIC ACID

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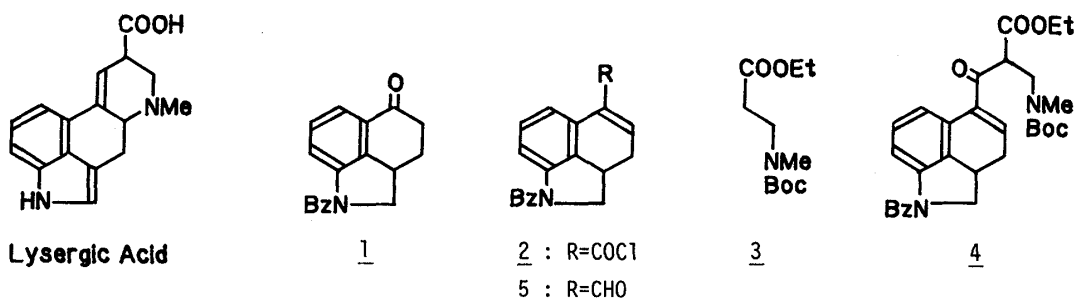
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A new and simple synthesis of ($\pm$)-lysergic acid from the aldehyde (5) is described involving aldol condensation with 3 in the presence of LDA as a key reaction.

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 ($\pm$)-lysergic acid by a modified Ramage method using tetrahydroindeno[2,1-b]pyridine derivatives.³⁾

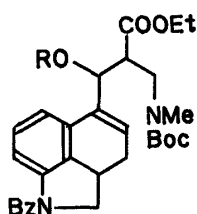
The ketone (1)²⁾ was converted to the acid chloride (2) via the six-step route described previously.⁴⁾ Preparation of the anion of 3 (LDA/THF/-78°C) and its reaction with 2 did not lead to the desired formation of β -keto ester (4) contrary to the model experiment.⁴⁾ However the aldol condensation of the anion of 3 with the aldehyde (5),²⁾ prepared by hydrogenolysis of 2 [10% Pd-BaSO₄/H₂/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/Et₃N/CH₂Cl₂) 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 ¹H-NMR) in 42.4% overall yield from 6 and 11⁶⁾ in 6.8% overall yield from 6, mp 178-180°C (from EtOAc); IR (KBr) 1710, 1645 cm⁻¹; UV (C₂H₅OH) 267 (4.09), 293 nm (3.95); ¹H-NMR (CDCl₃) 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-



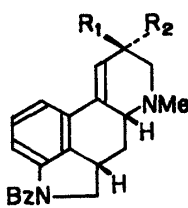
Bz=Benzoyl, Boc=*tert*-Butoxycarbonyl

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 ($\text{C}_2\text{H}_5\text{OH}$) 254 (4.51), 307 nm (3.80); $^1\text{H-NMR}$ (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 ($\text{MeOH}/\text{conc. HCl}/\text{reflux}$) of 8 and esterification ($\text{MeOH}/\text{dry HCl gas}/\text{r.t.}$) followed by mild benzoylation (BzCl/MeOH) afforded 10, mp 165-168°C, whose IR and $^1\text{H-NMR}$ spectra are identical with those of the authentic sample prepared in the course of the synthesis of ($\pm$)-lysergic acid by Ninomiya.⁷⁾

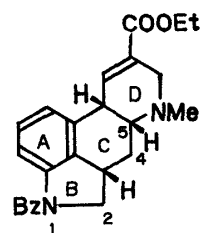
Thus, we have succeeded in developing a simple synthesis in few steps of ($\pm$)-lysergic acid in good overall yield.



6 : R=H
7 : R= SO_2Me



8 : $\text{R}_1=\text{COOEt}$, $\text{R}_2=\text{H}$
9 : $\text{R}_1=\text{H}$, $\text{R}_2=\text{COOEt}$
10 : $\text{R}_1=\text{COOMe}$, $\text{R}_2=\text{H}$



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- 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 $^1\text{H-NMR}$ 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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