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A NEW SYNTHESIS OF (±)-LYSERGIC ACID

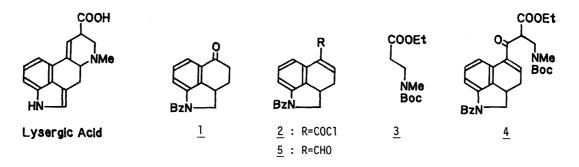
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A new and simple synthesis of $(\frac{1}{2})$ -lysergic acid from the aldehyde $(\underline{5})$ is described involving aldol condensation with $\underline{3}$ in the presence of LDA as a key reaction.

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 $^{[a-le)}$ since the first success by Woodward in 1956. Among these, our attention was focused on the Ramage method 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. $^{[a]}$

The ketone $(\underline{1})^2$ was converted to the acid chloride $(\underline{2})$ <u>via</u> the six-step route described previously. Preparation of the anion of $\underline{3}$ (LDA/THF/-78°C) and its reaction with $\underline{2}$ did not lead to the desired formation of $\underline{6}$ -keto ester $(\underline{4})$ contrary to the model experiment. However the aldol condensation of the anion of $\underline{3}$ with the aldehyde $(\underline{5})$, prepared by hydrogenolysis of $\underline{2}$ [10% Pd-BaSO₄/H₂/N,N-dimethylaniline/toluene-EtOAc(1:1)/70-80°C], afforded the alcohol $(\underline{6})$ in 99% yield as a diastereoisomeric mixture. This was converted (MsC1/Et₃N/CH₂C1₂) into the mesylate $(\underline{7})$. Without purification this substance was subjected to the de-<u>tert</u>-butoxycarbony-lation 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 $\underline{8}/\underline{9}$ (2:1 by 1 H-NMR) in 42.4% overall yield from $\underline{6}$ and $\underline{11}^{\underline{6}}$ in 6.8% overall yield from $\underline{6}$, mp 178-180°C (from EtOAc); IR (KBr) 1710, 1645 cm⁻¹; UV (C₂H₅OH) 267 (4.09), 293 nm (3.95); 1 H-NMR (CDCl₃) δ 1.30 (3H, t, \underline{J} =7.3 Hz), 1.54 (1H, td, \underline{J} =13 and 3 Hz), 2.46 (3H, s), 2.82 (1H, q, \underline{J} =3.6 Hz), 2.98 (1H, dt, \underline{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 (C₂H₅OH) 254 (4.51), 307 nm (3.80); H-NMR (CDCl₃) δ 1.31 (3H, t, \underline{J} =7.3 Hz), 1.39 (1H, q, \underline{J} =11.5 Hz), 2.50 (3H, s), 2.67 (1H, t, \underline{J} =11.5 Hz), 3.04 (1H, br d, \underline{J} =11.5 Hz), 3.26 (1H, dd, \underline{J} =11.5 and 6.1 Hz), 3.41 (1H, m), 3.62 (1H, m), 3.70 (1H, t, \underline{J} =11 Hz), 4.22 (2H, q, \underline{J} =7.3 Hz), 6.55 (1H, s), and 7.26-7.60 (8H, m). Hydrolysis (MeOH/conc. HC1/reflux) of $\underline{8}$ and esterification (MeOH/dry HCl gas/r.t.) followed by mild benzoylation (BzC1/MeOH) afforded $\underline{10}$, mp 165-168°C, whose IR and $\underline{1}$ H-NMR spectra are identical with those of the authentic sample prepared in the course of the synthesis of ($\underline{1}$)-lysergic acid by Ninomiya. 7)

Thus, we have succeeded in developing a simple synthesis in few steps of $(\frac{1}{2})$ -lysergic acid in good overall yield.

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