47. Total Synthesis of (±)-Lysergic Acid by an Intramolecular Imino-*Diels-Alder* Reaction

Preliminary communication

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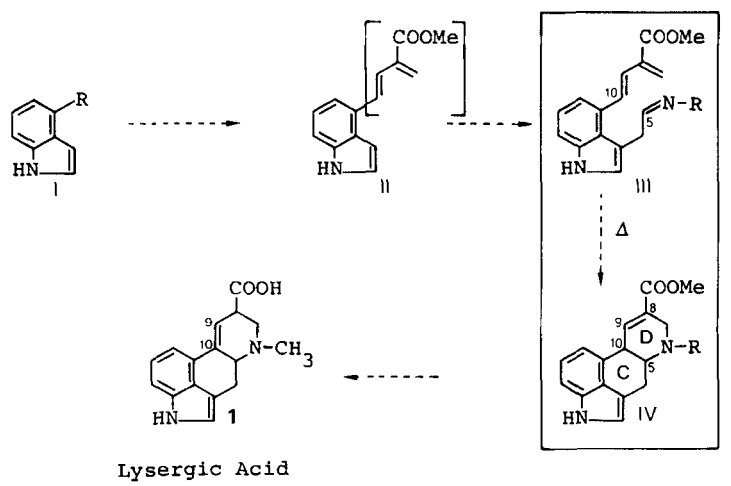
(4.II.81)

Summary

(±)-Lysergic acid (**1**) has been synthesized from 4-hydroxymethyl-1-tosylindole (**2**) by a sequence of 9 steps. The crucial thermolysis **9** → **10** involves the *in situ*-generation of the transient diene III which undergoes an intramolecular cycloaddition to a C,N-double bond at 200° and at low stationary concentration of III.

Lysergic acid, obtained by alkaline hydrolysis of ergot peptide alkaloids or more recently by isomerization of paspalic acid[1]), has been shown to have structure **1** [2]. Its derivatives show a fascinating spectrum of pharmacodynamic actions which led to the established use of various valuable drugs in human therapy [3]. Previous total syntheses of (±)-**1** have been carried out *via* 2,3-dihydroindole intermediates ultimately requiring a dehydrogenation step [4].

Scheme 1



Lysergic Acid

[1]) 6-Methyl-8-ergolene-8-carboxylic acid (paspalic acid), prepared by saprophytic cultivation of appropriate ergot strains in fermenters [1], as well as the C(8)-epimer of **1** (isolysergic acid) isomerize readily to lysergic acid in basic medium [1] [2].

0018-019X/81/2/0478-04$01.00/0

We now report a different synthesis of (±)-**1** which compares favorably with the former ones in terms of efficiency and length; in analogy to our recently disclosed approach to chanoclavines [5], the indole nucleus was kept intact throughout the entire reaction sequence. Our strategy *(Scheme 1)* relies on concomitant formation of the rings C and D by an intramolecular *Diels-Alder* reaction III → IV[2]) followed by isomerization of the C(8),C(9)-double bond to the more stable C(9),C(10)-position[1]).

To prepare the key-precursor III, several difficulties, particularly due to the instability of the 2-carbomethoxy-diene moiety, had to be resolved[3]). We therefore decided to start from a suitably 4-substituted indole I and to attach the diene unit in a protected form (I → II) which would not interfere with the subsequent introduction of the iminomethyl chain at position 3. Thermal liberation of the labile diene unit should permit its spontaneous interception by the internal imino group[2]).

Following this plan, 4-hydroxymethyl-1-tosylindole (**2**) [11] was converted (2 mol-equiv. PPh_3/CBr_4, DMF, 20°, 30 min) to the crystalline bromide **3**[4]) (97% yield, m.p. 133–134°) which on treatment with tributylphosphine (1.4 mol-equiv. in refluxing benzene, 2 h) gave the solid phosphonium bromide **4**[5]) (100% yield, m.p. 104–106°).

Formylation of methyl bicyclo[2.2.1]hept-5-enyl-2-carboxylate [12] by successive treatment with LDA (1.1 mol-equiv., THF, −75°, 1 h) and methylformate (2.4 mol-equiv., THF, −75°, 2 h) followed by chromatography (SiO_2) furnished the *exo*-formyl compound **5**[4]) (68% yield) together with methyl *cis*-4,4a,5,7a-tetrahydrocyclopenta[b]pyran-3-carboxylate[6]) (15% yield). *Wittig* reaction of this mixture with 1 mol-equiv. of the phosphorane derived from **4** ($NaCH_2S(O)CH_3$, DMSO, 20°, 16 h) furnished stereoselectively the (*E*)-vinylindol **6**[4]) (62% yield, m.p. 148–150°). Removal of the *N*-tosyl group by heating a solution of **6** in 2N methanolic NaOH furnished the vinylindol **7**[4]) (m.p. 78–79°, 95% yield) which underwent a *Michael* addition to nitroethylene [13] giving **8** in 24% yield. More efficiently (48% yield), the C(3)-functionalization **7** → **8** was accomplished in two steps by a *Mannich* reaction (HOAc, 40% aq. Me_2NH-solution, 36% aq. CH_2O-solution, 20°, 2 h) followed by treatment of the crude *Mannich* product with 10 mol-equiv. of nitromethane and 1.2 mol-equiv. of dimethyl acetylenedicarboxylate [14] at 20° for 5 h.

Transformation of the nitro compound **8** to the oxime ether **9** was achieved in one operation by reduction of the sodium nitronate derived from **8** with an excess solution of $TiCl_3/NH_4OAc$ in $MeOH/H_2O$ 3:1 at 20° for 2 h [15]

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[2]) Intramolecular *Diels-Alder* reactions involving iminodienophiles are still not widely recognized [6]; for the first example see [6a]. For recent reviews on intramolecular [4+2] cycloadditions and on bimolecular imino-*Diels-Alder* reactions see [7] and [8], respectively.

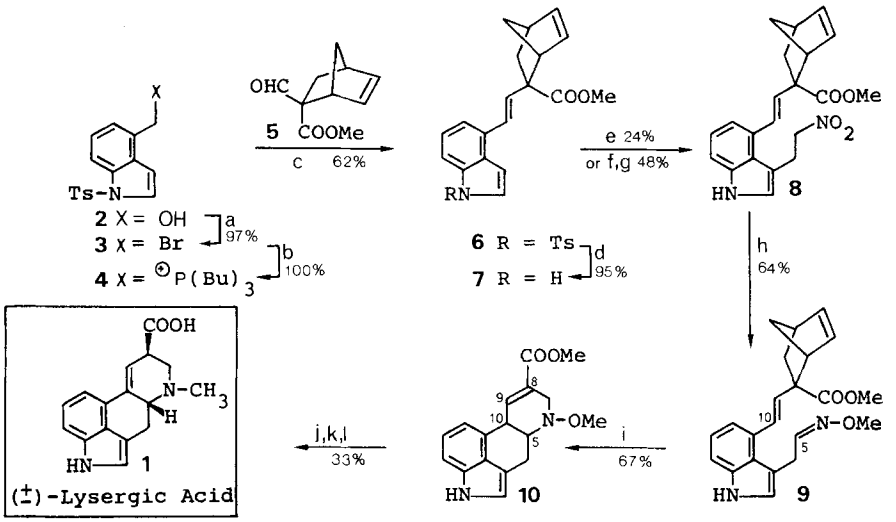
[3]) 2-Carbomethoxy-1,3-dienes dimerize spontaneously [9]. For their *in situ*-generation from dihydrothiophene precursors see [10].

[4]) IR.-, ^{1}H-NMR.- and mass spectra are in full agreement with the assigned structure.

[5]) Compound **4** was characterized by IR., ^{1}H-NMR. and elemental analysis (C,H,N).

[6]) This side product arising from a SiO_2-promoted retro-*Claisen* rearrangement of the minor *endo*-formyl isomer of **5** did not interfere with the subsequent *Wittig* reaction **5** → **6** and was fully characterized[4]) after chromatographic separation from **6**.

Scheme 2



a) CBr_4, PPh_3, DMF; b) PBu_3, C_6H_6, 80°; c) NaH, DMSO; d) NaOH, MeOH; e) $CH_2{=}CH{-}NO_2$, toluene, 25°, 66 h; f) aq. CH_2O-solution, Me_2NH; g) $MeNO_2$, $MeOOC{-}C{\equiv}C{-}COOMe$, 20°; h) 1. NaOMe, MeOH, 2. $TiCl_3/NH_4OAc$, $H_2N{-}OMe$, $MeOH/H_2O$ 3:1; i) 200°, trichlorobenzene; j) $MeOSO_2F$, CH_2Cl_2, 20°; k) Al/Hg, THF/H_2O 2:1; l) 0.5N KOH, $EtOH/H_2O$, under reflux.

in the presence of *O*-methylhydroxylamine (3 mol-equiv.). Under these reaction conditions, which permit instantaneous condensation of the labile 3-indolyl acetaldehyde with *O*-methylhydroxylamine, the stable oxime ether **9**[4]) was obtained in 64% yield[7]) as a 2:3-mixture of *syn*- and *anti*-isomers.

We now proceeded to the crucial thermolysis of **9**. It was hoped that a *retro-Diels-Alder* reaction would release the diene unit which might then preferentially add to the imino bond. Disappointingly, heating a 0.3% solution of **9** in bromobenzene under reflux for 1 h led quantitatively to at least three isomeric dimers of III (R = OMe). However, owing to the intramolecular nature of the desired addition, the mutually unreactive diene and dienophile should be forced to undergo cycloaddition by heating **9** to a higher temperature while keeping the stationary concentration of the transient diene III as low as possible. Accordingly, a 1% solution of **9** in 1,2,4-trichlorobenzene was added over 5 h by means of a syringe drive into preheated (200°) 1,2,4-trichlorobenzene under argon. Subsequent chromatography furnished the 8-ergolene **10**[4])[8]) as a 2:3 mixture of diastereoisomers in 67% yield. Replacement

[7]) When the modified *Nef*-reaction [15] of **8** and the oximation of the resulting indolyl acetaldehyde were carried out separately **9** was obtained in only 35% yield.

[8]) Compound **10** showed the following spectral data: UV. (MeOH, λ_{max} in nm ($\log\varepsilon$)): 224 (4.18), 274 (3.81). – IR. (CH_2Cl_2, λ_{max} in cm^{-1}): 3500*m*, 1720*s*, 1450*m*, 1060*m*. – ^{1}H-NMR. (360 MHz, $CDCl_3$, 77°, internal standard tetramethylsilane ($\delta = 0$ ppm); abbreviations: *s* = singlet, *d* = doublet, *t* = triplet, *m* = multiplet, *J* = spin-spin coupling constant (Hz)): 2.89 (*d*×*d*, *J* = 10 and 15, 0.4 H); 3.0–3.2 (1 H); 3.2–4.1 (3.6 H); 3.66 (*s*, 1.2 H); 3.70 (*s*, 1.2 H); 3.73 (*s*, 1.8 H); 3.8 (*s*, 1.8 H); 4.1–4.4 (1 H); 6.86 (*s*, 0.4 H); 6.88 (*s*, 0.6 H); 7.00 (*t*, *J* = 4, 0.4 H); 7.04–7.4 (3.6 H); 7.67 (br. *s*, 0.4 H); 7.84 (br. *s*, 0.6 H). – MS.: 299 (15, $M^+ + 1$), 298 (75, $C_{17}H_{18}N_2O_3^+$), 267 (85), 266 (27), 208 (44), 207 (100), 180 (56). Further chromatographic fractions contained the corresponding 6-methoxy-9-ergolenes together with dimers of III (R = OMe).

of the methoxy- at N(6) by a methyl-group was accomplished by methylation of **10** with methylfluorosulfonate (3 mol-equiv., CH_2Cl_2, 20°, 18 h) followed by hydrogenolysis of the resulting salt with amalgamated aluminium foil [16] (THF/H_2O 2:1, 0 to +5°, 18 h). The resulting 6-methyl-ergolene mixture was heated at reflux in 0.5 N KOH in ethanol/H_2O 1:1 under N_2 for 1 h. Concentration of the solution followed by acidification with 1 N HCl to pH 5.5 led to the precipitation of crystalline (±)-lysergic acid (**1**) (3 mg, 33% yield from **10**) showing ^{1}H-NMR. (360 MHz in d-pyridine or in d-DMSO), IR. (nujol or KBr), UV. (0.1 N NaOH) and mass spectra identical with those of racemic lysergic acid[9]) of natural origin [17].

Financial support of this work by the *Swiss National Science Foundation* and *Sandoz Ltd,* Basle, are gratefully acknowledged. We thank *Sandoz Ltd.* for a generous gift of 4-cyano-indole and for kindly providing a comparison sample of lysergic acid. Our thanks are due to Dr. *J. Ian Grayson* for carrying out experiments at a very early stage of the synthesis. We are grateful to Mr. *J.P. Saulnier* for careful NMR.-measurements.

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[9]) Optically pure (+)- and (−)-**1** have been previously obtained by resolution [18] of the racemic hydrazide of **1** [4a].