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SYNTHETIC INDOLE ALKALOIDS.II. A TWO STEP SYNTHESIS OF 4-CARBETHOXY-3-ETHYLENEDIOXYBUTYRALDEHYDE; A PENTACYCLIC ALKALOID PRECURSOR

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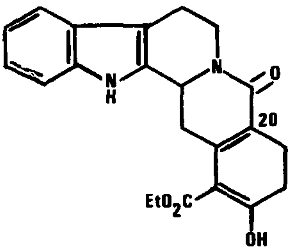
Our recently synthesized[1] pentacyclic ester lactam(1) represents a central intermediate for preparing, with proper structural variations, reserpinoid and yohimbinoid molecules[2] since its D/E ring junction reduces cis[1] while maintaining an epimerizable C_{20} hydrogen for possible conversion to D/E trans. However, its utility has been seriously limited by a lengthy eight step synthesis of low overall yield (1.5%). Of these eight synthetic steps, six were used to transform ethyl acetone dicarboxylate via its ketal(2) to the aldehydo ester(3). Reaction of 3 with tryptamine gave the tetracyclic keto lactam(4) which on treatment with carbethoxy methyl vinyl ketone gave 1.



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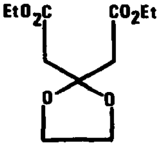

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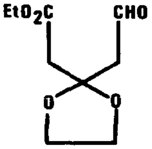

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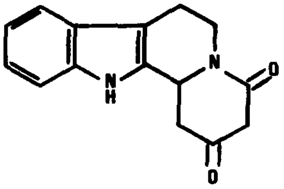

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It is the purpose of this communication to report a simple, easy two step synthesis of aldehydo ester(3) from ethyl acetone dicarboxylate via direct reduction of the blocked ketal(2) using diisobutyl aluminum hydride(DIBAL-H)[3] at low temperature, thus making our pentacyclic intermediate(1) readily available for exploratory synthesis in only four synthetic steps from ethyl acetone dicarboxylate.

The first step in our two step conversion involves, as before,[1] the blocking of ethyl acetone dicarboxylate's ketone function with ethylene glycol to give 2. However, by changing to BF_3 as a catalyst we have considerably increased the yield of 2 to 53%. Thus, 1000 ml. of dry benzene, 170 g. (0.84 mol) of freshly distilled ethyl acetone dicarboxylate, 104 g. (1.68 mol) of ethylene glycol and 6 ml. of boron trifluoride etherate when refluxed for 24 hours under a Dean-Stark phase separating apparatus gave after the usual workup[1] 53% of 2. The second step involves the controlled reduction of one ester function of 2 with DIBAL-H to give 3. Thus, to a stirred solution of 12.3 g. (0.05 mol) of ketal(2) in 400 ml. of a 1:1 solution of CH_2Cl_2 and anhydrous Et_2O, cooled to -78° (acetone-dry ice) was added dropwise, over 45 minutes, 34 ml. (0.05 mol) of a 1.47M solution of DIBAL-H in toluene. After stirring for one hour at -78°, 1.6 g. (0.05 mol) of absolute methanol was slowly added, followed in 15 minutes by 2.7 g. (0.15 mol) of water in 4 ml. of methanol. After filtration and drying, the solvent was removed to give 10.4 g. of a mixture of 2,3 and some blocked dialdehyde. The residue was vigorously stirred for 45 minutes with 15 ml. of saturated aqueous sodium bisulfite solution. After benzene extraction and drying, concentration gave 4.3 g. of blocked starting diester(2). The bisulfite solution, after 10% sodium carbonate solution had been added to make the solution basic (pH 9), was extracted with chloroform to give after the usual workup 4.3 g. (65.6%) of blocked aldehydo ester(3). Mixture melting point of 3's 2,4-dinitrophenylhydrazone with an authentic sample[1] was undepressed.

In the above process, overreduction of 2 to give the dialdehyde occurred in about 23% yield as determined by n.m.r., but the dialdehyde could only be recovered as the disemicarbazone. When 31.7 g. (0.127 mol) of 2 in 600 ml. of dry toluene was cooled to -78° and 170 ml. (0.262 mol) of a 1.54M solution of DIBAL-H in toluene was added dropwise, and then stirred for one hour, there was obtained, after the usual workup, 15.0 g. of the dialdehyde of 2 in 75% yield. Thus, when sufficient excess DIBAL-H was used the dialdehyde was readily obtained in good yield. Simple hydrolysis of the ketal group of the blocked dialdehyde produced chiefly γ-pyrone.

References

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