Total Synthesis of Chanoclavine I

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A totally new synthesis of ergoline related systems and a stereoselective synthesis of the ergot alkaloid chanoclavine I has been accomplished from indole-4-carboxaldehyde as follows.

The key starting material indole-4-carboxaldehyde was synthesized from 2-methyl-3-nitrobenzoic acid efficiently based on the straightforward extension of a general indole synthesis patented by Leimgruber and Batcho. Indole-4-carboxaldehyde was reacted with Wittig reagents to provide the vinyl indole 6 and 7 or to yield, after reduction (AlH_3) and O-acylation, indole 8′. These compounds could be converted readily into gramine derivatives by exposure to N,N′-dimethyliminium chloride. Reaction of the gramine compounds with excess nitromethane and dimethyl acetylenedicarboxylate led to the key 3,4-disubstituted indole 13a-13c. Using a procedure developed by Mukaiyama for the conversion of nitro groups to nitrile oxides, the indole 13a-13c could be readily converted to the iosxazolines 14a-14c in high yield (70-90%). After protecting the indole nitrogen by acylation, the moderately basic nitorgen of the isoxazoline was now methylated by Meerwein's reagent, and the intermediate salt was reduced with sodium borohydride. Because of the acetate group of 14c was found to interfere with this cinversion, the hydroxyl group was accordingly deprotected and then reprotected as its silyl ether. Compound 14c was an approximately 1:1 mixture of cis and trans-fused products. Desilylation of the hydroxyl group and scission of the nitrogen oxygen bond of 15b afforded the aminodiol 16a (94% overall). Triacetylation of this compound followed by selective O-deacetylation afforded 16a (78% overall). Periodate cleavage of free diol led to the sensitive key aldehyde. Reaction of the aldehyde 17 with ethyl-2-(triphenylphosphoranylidene) propionate afforded the unsaturated ether 18a(50% overall). After N-deacetylation, completion of the synthesis of (±)-chanoclavine I was accomplished by reducing 18b to allylic alcohol by treatment with aluminum hydride (78% overall). Comparison of synthetic material with natural chanoclavine I was made through the N,O-diacetylated compound.