Synthesis of tetracyclic spiroindolizidine-oxindole

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Abstract: Spirooxindole is a structural feature found in many biologically active alkaloids. For examples, rhynchophylline isolated from Uncaria sinensis exhibits antihypertensive and neuroprotective activities and mitraphyline isolated from Mitragyna speciosa or ‘Kratom’ is being investigated for its antiproliferative and cytotoxic effects in human breast cancer, sarcoma as well as lymphoblastic leukaemia cell lines. We synthesized two C12 a diastereomers of indoloquinolizidinone 1 in 5 steps from L-glutamic acid and tryptamine. These indoloquinolizidinones underwent oxidative ring contraction upon treatment with NBS in THF/H₂O and catalytic TFA to give spiroindolizidine–oxindole 2 in good yields. The dibenzylamino group was removed via Cope elimination by treatment with m-CPBA. The resulting cyclic enamidine functionality in compound 3 is suitable for further synthetic steps to install substituents for synthesis of rhynchophylline and mitraphylline.

Keywords: Spiroindolizidine-oxindole; Indoloquinolizidine; Oxidative ring contraction; Synthesis