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Synthesis of a Novel, Conformationally Restricted Analog of Tryptophan

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Key Words: Conformationally restrained tryptophan analog, diazoketone-$BF_3 \cdot Et_2O$ catalyzed intramolecular cyclization, cycloalk[b]indolones.

Abstract: *The synthesis of a new, conformationally restrained analog of tryptophan, 1,2,3,4-tetrahydro-2-amino-2-carboxy-cyclopent[b]indole (5) is described. The key step involves the $BF_3 \cdot Et_2O$ catalyzed intramolecular cyclization of α-diazoketone 2b into the 1,2,3,4-tetrahydro-cyclopent[b]indol-2-one (3).*

Conformationally restricted aminoacids are actively sought. They can be incorporated in peptides in place of the corresponding aminoacid thus becoming stereochemical probes for bioactive conformations or selective interactions. They can confer improved metabolic stability, increase the binding stability to receptors or exhibit enzyme inhibiting properties.

As a part of a program directed to the preparation and biological evaluation of conformationally restrained analogs of aminoacids [1] we become interested in the synthesis of cyclic analogs of tryptophan having the aminoacidic moiety relatively fixed in space with respect to the planar indole nucleus. A derivative fulfilling this requisite, 3-amino-1,2,3,4-tetrahydrocarbazole-3-carboxylic acid was reported previously and shown to be a competitive inhibitor of α-chimotrypsin.[2] We report now the first synthesis of the structurally related, conformationally more restrained 1,2,3,4-tetrahydro-2-amino-2-carboxy-cyclopent[b]indole (5). A survey of the literature revealed that while a variety of methods have been developed for the synthesis of 1-oxo- [3] and 3-oxo-1,2,3,4-tetrahydro-cyclopent[b]indole derivatives,[4,5] 1,2,3,4-tetrahydro-cyclopent[b]indol-2-one (3), key to our synthesis, was still unknown.

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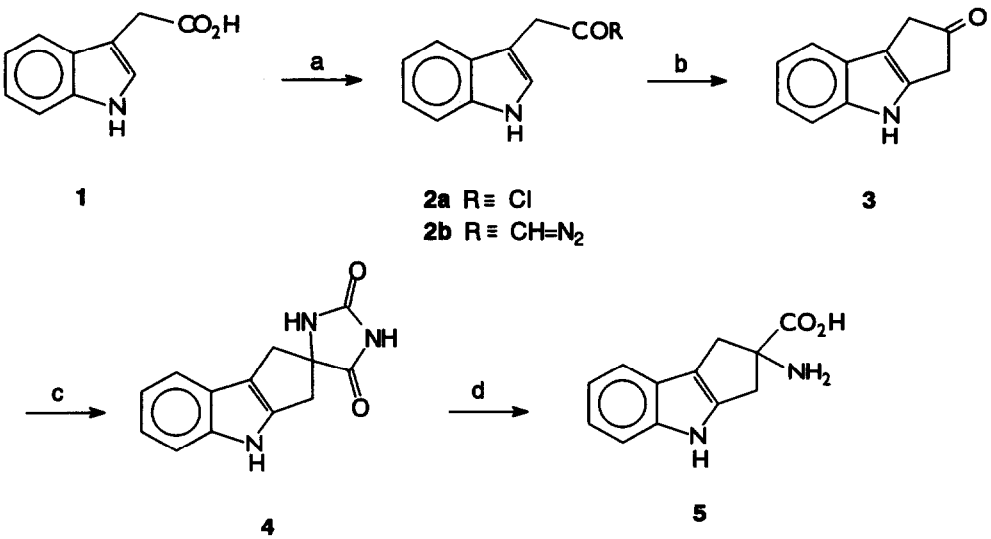
After exploring a number of routes, we discovered that the sequence outlined in Scheme I provided an expeditious solution to the problem.

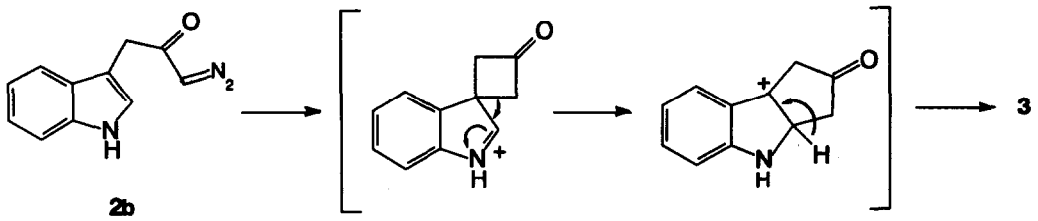
Scheme 1



(a) : i) PCl_5 , Et_2O; ii) CH_2N_2 , Et_2O; (b) : $BF_3 \cdot Et_2O$; (c) : KCN , $(NH_4)_2CO_3$, DMF ^-H_2O; (d) : i. $Ba(OH)_2$; ii. H_2SO_4; iii. Dowex 1x8, 100–200 mesh, AcO^- form.

Accordingly, 3-indoleacetic acid (**1**) was reacted with phosphorous pentachloride in anhydrous ether at 0 °C for 1 h under vigorous magnetic stirring in a nitrogen atmosphere. The reaction mixture was concentrated and then diluted with cold (0 °C) hexane. After filtration, the resulting solution was cooled at -78 °C to give the acyl chloride **2a** [6] with 72% yield. When **2a** was treated with diazomethane at 0 °C for 16 h, the diazomethylketone **2b** was formed with 57% yield. Following treatment of **2b** with boron trifluoride etherate in ether at 0 °C for 2.5 h and stirring overnight of the resulting mixture at room temperature gave the desired 1,2,3,4-tetrahydrocyclopent[b]indol-2-one as a sole product in 92% yield. The mechanism, depicted in Scheme II, presumably involves the initial cyclization of **2b** leading to the formation of a spiroindolenine which is rapidly unravelled to the corresponding cyclopentenone derivative (**3**).[7]

Scheme 2



Reaction of ketone 3 with potassium cyanide and ammonium carbonate in DMF-water in a bomb at 120 °C for 2 h produced the spirohydantoin [8] 4 with 68% yield. Finally, the amino acid 5 was obtained by heating an aqueous solution of 4 and barium hydroxide octahydrate in a bomb at 120 °C for 5 h followed by purification by ion exchange resin chromatography on Dowex 1x8 and elution with 0.3N acetic acid (53% yield). The structure of 5 was confirmed by analytical and spectroscopic data.[9,10] The application of the sequence 1 ⟶ 5 to the preparation of novel, homologous cycloalk[b]indolones, as well as the biological characterization of 5 are currently under way.

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9. Selected spectroscopic data for compounds **2b**, **3**, **4**, **5**.
2b: ^{1}H-NMR ($CDCl_3$) δ 3.65 (2H, s, CH_2CO); 5.10 (1H, s, CHN_2); 6.90-7.50 (5H, m, aromatic 's); 8.50 (1H, br s, NH).
3: mp 184-6 °C; ^{1}H-NMR ($CDCl_3$) δ 3.30 (2H, s, CH_2); 3.40 (2H, s, CH_2); 6.80-7.30 (5H, m, NH and aromatic 's).
4: mp 281-2 °C; ^{1}H-NMR ($CDCl_3$ + CD_3OD, 9:1) δ 3.06 and 3.40 (2H, 2d, J= 14.8 Hz, CH_2); 3.10 and 3.50 (2H, 2d, J= 16.3 Hz, CH_2); 7.05 and 7.35 (4H, 2m, aromatic 's); ^{13}C-NMR (CD_3OD) δ 39.57; 39.87; 74.96; 113.68; 116.39; 120.05; 121.21; 122.71; 126.43; 140.74; 143.92; 159.83; 181.52.
5: mp 170 °C (d); ^{1}H-NMR (D_2O) δ 3.07 and 3.45 (2H, 2d, J= 15.9 Hz, CH_2); 3.13 and 3.58 (2H, 2d, J= 17.3 Hz, CH_2); 7.05 and 7.38 (4H, 2m, aromatic 's); ^{13}C-NMR (CD_3OD) δ 37.54; 37.80; 69.94; 112.95; 114.59; 119.09; 120.49; 122.17; 125.16; 139.10; 143.34; 173.40.

10. Chiral thin layer chromatography (Chiralplate , Macherey-Nagel art. 811057) of **5**, performed in MeOH-H_2O-CH_3CN (1:1:4) using 1% aqueous ninhydrin as spraying reagent, reveals the two enantiomeric amino acids as two spots with rf. 0.63 and 0.53, respectively.

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