

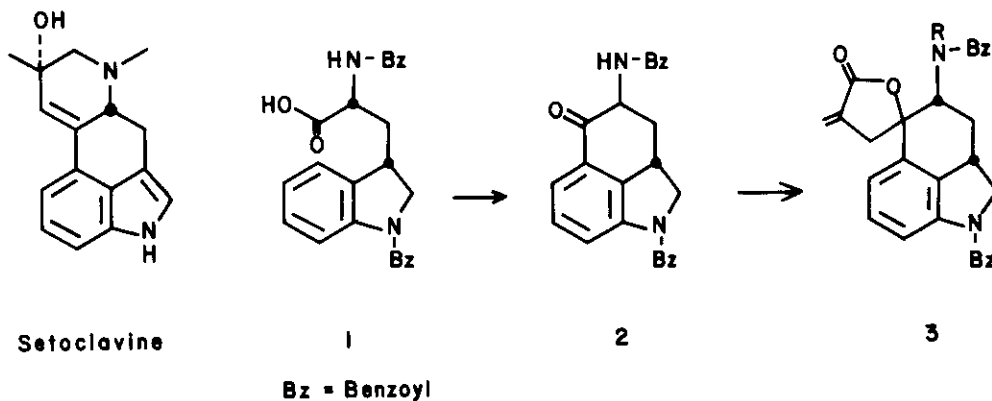
SYNTHESIS OF SETOCLAVINE

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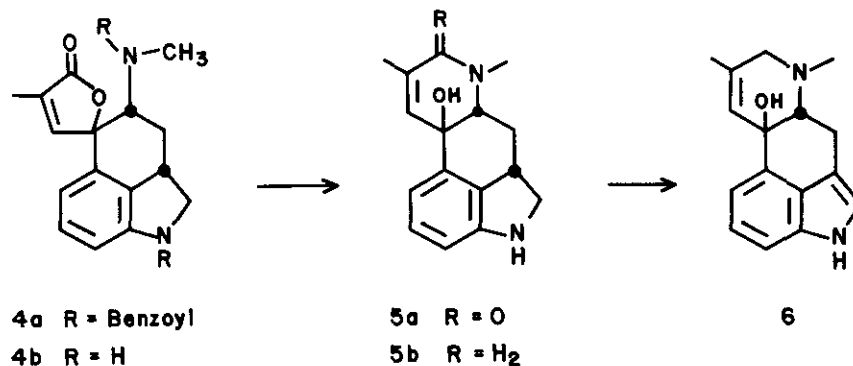
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Abstract - The first total synthesis of the ergot alkaloid setoclavine is described. Tryptophan is the starting material and methods used are of some generality for the synthesis of other ergot alkaloids.

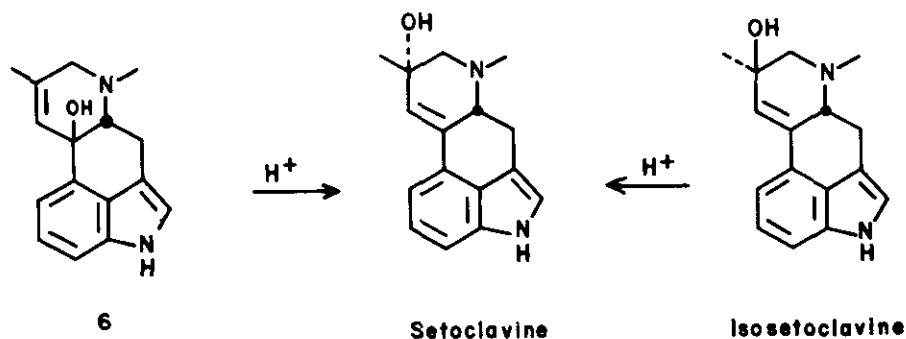
Setoclavine, despite its relatively simple structure, has been prepared only through formal synthesis¹ or by isolation from natural sources.² Our program of synthesis of ergot alkaloids from tryptophan has now led to the preparation of (+)-setoclavine and we report here our methods.



Tryptophan, blocked as its dihydro, dibenzoyl derivative³ **1**, was converted to the ketone **2** from which the methylene lactone **3** was obtained as previously described.⁴ Double bond isomerization (RhCl_3)⁵ then N-alkylation (MeI , NaH) gave the butenolide **4a**, m.p. $>275^\circ\text{C}$, which was deblocked⁶ ($\text{Et}_3\text{O}^+\text{BF}_4^-; \text{H}_3\text{O}^+$) to the amine **4b**, m.p. 194°C (57% from **3**). Treatment with base (NaOMe/HOMe) led to the lactam **5a** which was reduced (LAH/THF) to the amine **5b**. Oxidation (MnO_2) of the indoline yielded **6** (45% from **4b**), which rearranged quantitatively to (+)-setoclavine, m.p. 206°C . Such



rearrangements had been observed with quite similar structures^{7a} and involve the capture of nucleophiles at C₈ on the less hindered α face. In accord with this reasoning, (\pm)-isotoclavine^{7b} rearranged cleanly to (\pm)-setoclavine when we treated a sample with 1N HCl.



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