Synthesis of (−)-Indolactam V

Mark Mascal and Christopher J. Moody*

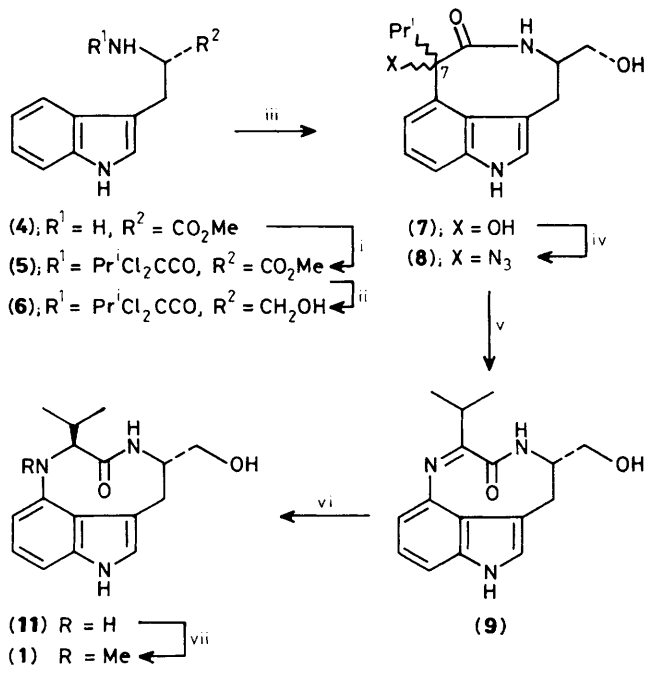
Department of Chemistry, Imperial College of Science and Technology, London SW7 2AY, U.K.

A stereospecific seven-step synthesis of (−)-indolactam V (**1**) from tryptophan methyl ester *via* the pyrrolobenzazocines (**7**) and (**8**) is described.

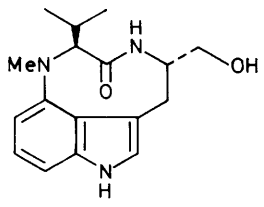
Indolactam V (**1**), isolated in 1984,[1] is one of a family of naturally occurring compounds containing a nine-membered lactam bridging the indole 3- and 4-positions. This group of compounds, which includes lyngbyatoxin A[2] (**2**), and the teleocidins[3] *e.g.* (**3**), are of considerable interest because of their potent tumour promoting activity. To date, all efforts to synthesise this class of compound have centred around precursors which require functionality in both the indole 3- and 4-positions, which is then used to build up the lactam ring by formation of the amide bond. We now report a short, seven step synthesis of (−)-indolactam V (**1**), which is fundamentally different from existing approaches, and involves, as key steps, the photocyclisation[4] of a simple tryptophan derivative followed by a nitrene-mediated ring expansion.

The key intermediate in our synthesis (Scheme 1) is the 7-hydroxy-7-isopropylpyrrolo[4,3,2-*f*,*g*]benzazocine (**7**), easily prepared in quantity in just three steps from (−)-tryptophan methyl ester.[4] Thus the commercially available ester (**4**) was acylated with 2,2-dichloro-3-methylbutanoyl chloride to give the dichloroisovaleryl tryptophan ester (**5**) (97% yield; m.p. 96—97 °C). Reduction of the ester with sodium borohydride occurred smoothly at room temperature to give the corresponding tryptophanol (**6**) (83% yield), photocyclisation[4] of which in aqueous acetonitrile gave (**7**) (55—60% yield) as a 4:1 mixture of epimers at C-7. The major epimer (m.p. 197—198 °C) is assigned as having the isopropyl group *trans* to the hydroxymethyl substituent, although separation of the isomers was unnecessary as stereochemistry at this centre is subsequently destroyed.

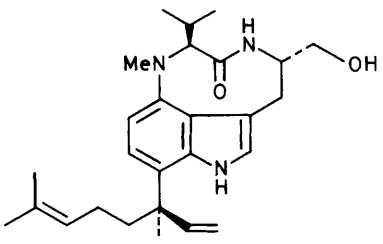
In order to effect the required ring expansion reaction, the tertiary alcohol (**7**) had to be converted into the corresponding azide (**8**), and several methods were attempted. The procedure which has given the best results to date involves treatment of (**7**) with a chloroform solution of hydrazoic acid (*ca.* 1.5 M) at room temperature. Facile dehydration of the tertiary alcohol and intramolecular cyclisation involving the primary alcohol group limit the extent to which the azide introduction reaction can be driven; the modest yields of the azide (**8**) (*ca.* 35% based on conversion) are, however, compensated by the easy availability of the alcohol (**7**).



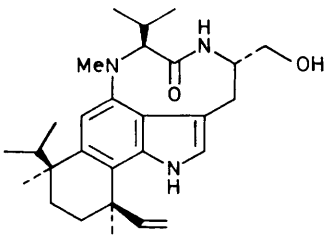
Scheme 1. *Reagents:* i, Pr^iCl_2CCOCl, aq. $NaHCO_3$, CH_2Cl_2; ii, $NaBH_4$, EtOH; iii, *hv*, aq. MeCN; iv, NaN_3, CF_3CO_2H, $CHCl_3$; v, *hv*, MeCN; vi, $NaBH_3CN$, MeOH; vii, MeI, $NaHCO_3$, MeOH.



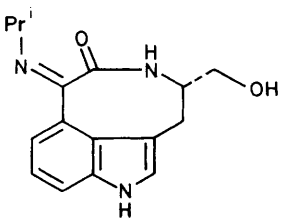
(**1**)



(**2**)



(**3**)



(**10**)

Irradiation of the azide (**8**) led to the required ring-expanded imine (**9**) (23% yield), resulting from migration of the aryl group to the electron deficient centre, along with the exocyclic imine (**10**) (28% yield) arising from the alternative isopropyl group migration. Treatment of the imine (**9**) with sodium cyanoborohydride resulted in stereoselective reduction† to give desmethyl indolactam V (**11**) {$[\alpha]_D$ −78.3° (*c* 0.30, MeOH); lit.[1d] −76.0° (*c* 0.72, MeOH)}, in 69% yield, methylation of which under literature conditions[1d] gave (−)-indolactam V (**1**) {$[\alpha]_D$ −136.0° (*c* 0.30, MeOH); lit.[1d] −134.5° (*c* 0.70, MeOH)}, which was identical (t.l.c., i.r. and 250 MHz ^{1}H n.m.r. spectroscopy) to an authentic (racemic) sample.

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† Although the epimers of desmethyl indolactam V (**11**) could not be separated, after methylation we were able to detect a maximum of 5% of *epi*-indolactam V by 250 MHz ^{1}H n.m.r. spectroscopy.

References

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3 S. Nakatsuka, T. Masuda, and T. Goto, *Tetrahedron Lett.*, 1987, **28**, 3671, and references therein.

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