Efficient Asymmetric Synthesis of Indolizidine Building Blocks

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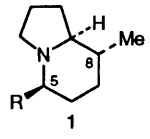
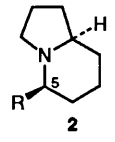
Intramolecular Friedel–Crafts acylation of a pyrrole derived from L-glutamic acid, followed by a highly selective hydrogenation, leads to either of the optically pure indolizidine alkaloid precursors **6** or **7**, depending on the catalyst.

In recent years there has been much activity in the biological evaluation of a series of alkaloids which are found in minuscule quantities in the skin extracts of the *Dendrobatidae* family of neotropical arrow poison frogs,[1] and, in particular, a sub-group of 5-substituted indolizidines has attracted attention. Alkaloids **1**, bearing a *trans* 8-methyl substituent, have all been isolated from dendrobatid frogs and have been shown to be among the most potent non-competitive blockers for nicotinic receptor channels.[2] One 8-substituted example **2a** of this series has also been isolated from frogs,[1] and, very recently, the first marine indolizidines were discovered in the tunicate *Clavelina picta*.[3] These compounds **2b** exhibit antimicrobial activity against several fungi and Gram-positive bacteria.[3]



1

a R = pentyl, pentenyl, pentynyl
b R = heptenyl, heptadienyl, hydroxyheptenyl



2

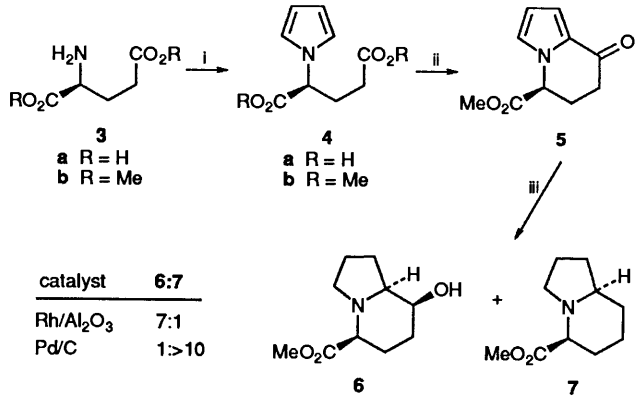
a R = propyl
b R = decenyl, decadienyl, decatrienyl

Although a number of syntheses of naturally occurring 5-substituted and 5,8-disubstituted indolizidines have been reported,[4] these syntheses generally suffer from at least one of the following drawbacks: (1) the side chains R are often incorporated early in the syntheses; this prohibits facile production of analogues; (2) most of the routes are too long to be of practical value, rather they are showcases for particular reactions of interest.

We describe here rapid asymmetric syntheses of indolizidines which are suitably functionalised for conversion into all known naturally occurring 5-substituted and 5,8-disubstituted indolizidines, as well as a wide range of synthetic analogues. Although our route uses adaptations of previously described methods it has a number of advantages. (1) The starting material is L-glutamic acid. (2) The resultant 5-substituent R is suitably functionalised for homologation to a range of derivatives. (3) The hydrogenation step leads selectively to either the 5-substituted or the 5,8-disubstituted series. (4) The resultant 8-substituent (hydroxy) is suitable for displacement by nucleophiles to yield a number of analogues.

Syntheses of the pyrrole derivatives **4** of glutamic acid **3a** have previously been described[5] but we found that an adaptation[6] of the original procedure gave more reliable results. Although intramolecular acylation of pyrroles has been described for a lower homologue of **4**[7] this method has not previously been applied to the synthesis of indolizine derivatives. Since cyclisation of **4b** with trimethylsilyl trifluoromethanesulfonate (TMSOTf) gave reasonable yields only with a large excess of the reagent, we turned to the diacid analogue **4a** and found that, on treatment with dry HCl in methanol, cyclisation proceeded smoothly with concomitant esterification of the non-acylating acid group to yield **5**.

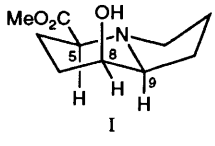
The facially directed hydrogenation of pyrrole derivatives is an established method for preparation of indolizidines.[6] Indeed, hydrogenation with either rhodium on alumina or palladium on charcoal produced the expected stereochemistry at C-9. The chemistry of C-8 was, however, strongly dependent on which catalyst was used, rhodium yielding predominantly the (*S*)-alcohol **6** [no (*R*)-alcohol was observed] and palladium the fully reduced indolizidine **7**.



Scheme 1 *Reagents and conditions:* i, 2,5-dimethoxytetrahydrofuran, sodium acetate, acetic acid, reflux (10 min), 50%; ii, dry HCl, MeOH, 20 °C (3 h), 50%; iii, H_2, catalyst (see Table in Scheme), 55 psi (16–24 h), quantitative conversion

The procedure outlined above was also used to transform 4-aminobutyric acid (GABA) **8** into racemic indolizidine **12** in three steps. When rhodium on alumina was used in the place of palladium on charcoal, a mixture of racemic 8-hydroxyindolizidines **11a** and **11b** was produced in a 2:1 ratio and no indolizidine was observed by NMR. Once again, the result of the hydrogenation was very effectively controlled by choice of catalyst (Scheme 2).

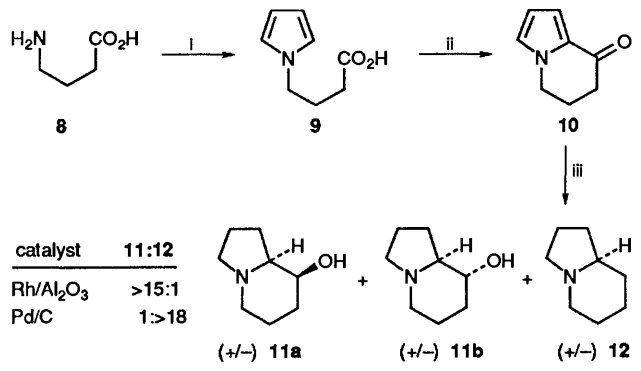
The IR and ^1H NMR spectra of compound **6** confirmed that the relative stereochemistries of C-5, C-8 and C-9 were, as expected, as shown in **I**. The ^1H NMR resonances due to



I

5-H, 8-H and 9-H (δ_H 2.81, 3.79 and 2.15, respectively) were essential for this analysis.

The observation of Bohlmann bands at 2810 cm^{-1} in the IR spectrum is diagnostic of a *trans* ring junction with the nitrogen lone-pair and 9-H in axial positions.[8]



Scheme 2 *Reagents and conditions:* as for Scheme 1

The lack of *trans* couplings to 8-H in the ^{1}H NMR spectrum, as evidenced by a small (8 Hz) line width of the unresolved multiplet, indicates that this proton is in an equatorial position.

The chemical shift of 5-H suggests an axial location, as judged by comparison with spectra of similar compounds.[8]

Upon irradiation at the resonant frequency of 9-H NOE effects were observed in the signals due to 5-H (2.5%) and 8-H (3.5%). This is consistent with these protons lying on the same face of the molecule with 5-H and 9-H in a 1,3-diaxial relationship.

Experimental

General Procedure for Formation of Pyrroles **4** *and* **9**.—A solution of **3** or **8** (0.02 mol) in acetic acid (150 cm^3) together with anhydrous sodium acetate (10.11 g, 0.123 mol) was heated to 70 °C and 2,5-dimethoxytetrahydrofuran (2.6 cm^3, 0.02 mol) was added to it dropwise. After 10 min (post addition) the solution was diluted with water (100 cm^3) and extracted with CH_2Cl_2 (diethyl ether for **4a**) (3 × 100 cm^3). The combined extracts were concentrated to afford the crude pyrrole, Kugelrohr distillation (~ 180 °C, 0.2 mmHg) of which afforded pure **4** or **9** (50% yield).

General Procedure for the Synthesis of Indolizine Derivatives **5** *and* **10**.—Dry HCl gas was bubbled through a solution of **4** or **9** (5.1 mmol) in dry methanol (150 cm^3) for 3 h after which the mixture was concentrated under reduced pressure and evaporated to dryness. Chromatography of the residue on silica gel with ethyl acetate–light petroleum (b.p. 40–60 °C) (1:1) as the eluent yielded the bicyclic compounds **5** and **10** (50% yield).

General Procedure for the Synthesis of the Indolizidines **6**, **7**, **11** *and* **12** *by Hydrogenation of Compounds* **5** *and* **10**.—A solution of **5** or **10** (1.19 mmol) in dry methanol (100 cm^3) containing conc. H_2SO_4 (4 drops) and catalyst (w/w with substrate) was hydrogenated (20 °C, 55 psi) for 16–24 h. The suspension was then filtered through a Celite pad and the solvent removed under reduced pressure. A solution of the residue in water (100 cm^3) was acidified to pH 1–2 (H_2SO_4) and washed with Et_2O (2 × 100 cm^3). The aqueous layer was then basified to pH 9–10 (Na_2CO_3) and extracted with CH_2Cl_2 (3 × 100 cm^3). The combined CH_2Cl_2 extracts were dried ($MgSO_4$) and evaporated to dryness to afford the indolizidines (quantitative conversion). Isomer ratios were determined by ^{1}H and ^{13}C NMR spectroscopy of crude product mixtures.

Compound **6** was isolated (66%) by preparative thin layer chromatography on alumina plates developed with ethyl acetate–light petroleum (b.p. 40–60 °C) (1:1). Compounds **7** and **12** required no purification. Compounds **11a** and **11b** were not separated but the mixture of diastereoisomers contained no other products.

Acknowledgements

We thank the SERC and the University of Warwick for financial support.

References

1 J. W. Daly, *Fortschr. Chem. Naturst.*, 1982, **41**, 205; J. W. Daly, C. W. Myers and N. Whittaker, *Toxicon*, 1987, **25**, 1023; T. Tokuyama, N. Nishimori, A. Shimada, M. W. Edwards and J. W. Daly, *Tetrahedron*, 1987, **43**, 643; T. Tokayuma, T. Tsujita, H. M. Garraffo, T. F. Spande and J. W. Daly, *Tetrahedron*, 1991, **47**, 5415.
2 J. W. Daly, Y. Nishizawa, W. L. Padgett, T. Tokuyama, A. L. Smith, A. B. Holmes, C. Kibayashi and R. S. Aronstam, *Neurochem. Res.*, 1991, **16**, 1213.
3 M. F. Raub and J. H. Cardellina, *Tetrahedron Lett.*, 1992, **33**, 2257.
4 The most important contributions up to 1991 were summarised by A. B. Holmes, A. L. Smith, S. F. Williams, L. R. Hughes, Z. Lidert and C. Swithenbank, *J. Org. Chem.*, 1991, **56**, 643. For some more recent examples see C. W. Jefford and J. B. Wang, *Tetrahedron Lett.*, 1993, **34**, 3119; A. Fleurant, J. P. Celerier and G. Lhommet, *Tetrahedron Asym.*, 1992, **3**, 695; Y. Shishido and C. Kibayashi, *J. Org. Chem.*, 1992, **57**, 2876; D. L. Comins and E. Zeller, *Tetrahedron Lett.*, 1991, **32**, 5889; H. J. Knolker, R. Boese and K. Hartmann, *J. Chem. Soc., Chem. Commun.*, 1991, 405; see also ref. 6.
5 C. Kashima, T. Maruyama, K. Harada, S. Hibi and Y. Omote, *J. Chem. Res.*, 1988, (*S*), 62; (*M*), 601.
6 C. W. Jefford, Q. Tang and A. Zaslona, *J. Am. Chem. Soc.*, 1991, **113**, 3513.
7 S. J. Box and D. F. Corbett, *Tetrahedron Lett.*, 1981, **22**, 3293.
8 P. E. Sonnet, D. A. Netzel and R. Mendoza, *J. Heterocycl. Chem.*, 1979, **16**, 1041.

Paper 3/04556K
Received 30*th July* 1993
Accepted 30*th July* 1993