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Stereoselective synthesis of (8*R*,8a*S*)-8-methylhexahydroindolizin-5-one

Paul Armstrong,[b] Gavin O'Mahony,[a] Paul J. Stevenson[a,*] and Andrew D. Walker[a]

[a]*School of Chemistry, Queen's University, Belfast BT9 5AG, Ireland*
[b]*CSS Ltd, Almac House, 20 Seagoe Industrial Estate, Craigavon BT63 5PW, Ireland*

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Abstract—Catalytic hydrogenation of dihydroindolizidinone occurred preferentially from the *endo*-face giving rapid entry to (8*R*,8a*S*)-8-methylhexahydroindolizin-5-one, a key intermediate in the synthesis of 5,8-disubstituted indolizidines and deoxypumiliotoxin 251H. The selectivity could be improved further by diimide reduction though this also resulted in some oxidation of the alkene to the diene. The basis of the unusual stereoselectivity in the diimide reduction is believed to be stereoelectronic in origin.

(8*R*,8a*S*)-8-Methylhexahydroindolizin-5-one **1** (Fig. 1) has emerged as an important intermediate in the synthesis of 5,8-disubstituted indolizidine alkaloids. Nucleophilic addition of organometallics to the amide followed by reduction of the intermediate iminium ion is a versatile method for introducing the 5-substitutent.[1] The first racemic synthesis of **1** assembled the δ-lactam fragment by a Beckmann rearrangement of a cyclopentanone oxime. Homochiral **1** has been prepared in an enantioselective synthesis involving a ring expansion of a cyclopentanone utilising an intramolecular Schmidt reaction.[2] Subsequent asymmetric approaches involve Sharpless asymmetric epoxidation of a trisubstituted allylic alcohol[3a] or addition of chiral allenyltitanium reagents to imines[3b] as the key steps.

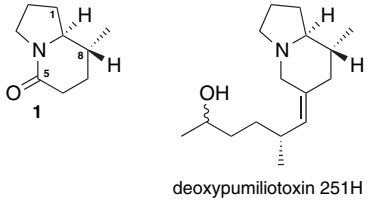
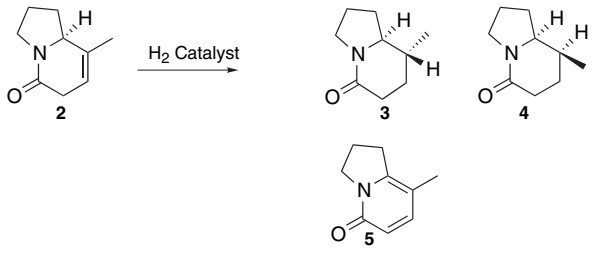


Figure 1. Indolizidine **1**, showing indolizidine numbering, and the proposed structure of deoxypumiliotoxin 251H.

The pumiliotoxin alkaloids, isolated from the defensive skin secretions of *Dendrobates* frogs have an indolizidine ring with a *Z*-exocyclic alkene at C6.[4,5] All have a methyl group at C8 and the different classes are distinguished by the oxygenation pattern in the six-membered ring. The vast majority of pumiliotoxins have a tertiary alcohol at C8 and the allopumiliotoxins have an additional hydroxyl group at C7. Recently, a new class of pumiliotoxin, devoid of the tertiary alcohol at C8, has been isolated and the structure has been tentatively assigned as deoxypumiliotoxin 251H (Fig. 1).[6] To date, no synthesis of the deoxypumiliotoxin 251H has been reported. Indolizidinone **1** is an ideal precursor for deoxypumiliotoxin 251H as the 6-alkylidene moiety could be introduced by Gallagher's[7] aldol methodology.

Scheme 1 outlines our new rapid approach to indolizidine **1**. We have previously reported the efficient preparation of the key dehydroindolizidine **2**,[8] using an alkene



Scheme 1.

Keywords: Indolizidines; Stereoelectronic; Cieplak effect.
* Corresponding author. Tel.: +44 02890974426; fax: +44 02890974687; e-mail: p.stevenson@qub.ac.uk

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metathesis reaction as the key step. Initially it was envisaged that if the γ,δ-double bond could be isomersised into conjugation with the amide carbonyl group then this would favour the isomer in which the C-8 methyl group was equatorial. Catalytic hydrogenation of the conjugated alkene would then give the desired indolizidine **1**. However, despite extensive experimentation, alkene **2** proved to be remarkably stable with respect to isomerisation when treated with a wide range of acids, bases and transition metal salts. In no case was any isomerisation to the conjugated compound observed.

Subsequently, reduction of the trisubstituted alkene **2** was carried out under a number of conditions and the results are annotated in Table 1. With catalytic hydrogenation, the best catalyst proved to be Pt/C and this gave a 3.6:1 mixture of **3**:**4** in quantitative yield from which a small amount of the major isomer **3** could be separated by careful flash chromatography. The spectral data for the major isomer **3** were in good agreement with the published values.[3] Further confirmation that the stereochemistry was correctly assigned came from proton NMR spectral data. In particular proton H8a was a triplet of doublets with coupling constants of 9.8 and 4.9 Hz, respectively, strongly suggesting that the 8-methyl group occupied an equatorial position. Saturation of the methyl resonance gave a NOE of 5.5% to H8a confirming this assignment.

The selectivity could be improved further using diimide as the reducing agent. Corey's hydrazine hydrate/hydrogen peroxide method[9] gave the reduced products **3**, **4** along with the oxidised product **5** in a ratio of 15:1:1, respectively, demonstrating that workable selectivities could be achieved. Unfortunately this reaction was tedious to perform, as a large excess of the reducing agents was required and the procedure had to be repeated four additional times to get the reaction to go to 70% completion. A separate work-up was required for each run lowering the overall yield to 48%. This probably reflects the reluctance of trisubstituted alkenes to undergo reduction with diimide.

The origin of the observed selectivities is intriguing. A review of the literature indicated that in reduction of the corresponding pyrrolizidines[10] and 6-substituted-1,2,3,3a,4,6a-hexahydropentalenes[11] the stereoselectivity was opposite to that observed with indolizidine **2**. The former substrates have a cis-ring junction giving rise to very distinct convex and concave, *exo*- and *endo*-faces, respectively. Not surprisingly, these substrates show exclusive reactivity on the *exo*-face. In the corresponding indolizidines and 7-substituted-2,3,3a,4,5,7a-hexahydro-1*H*-indenes the situation becomes more complex as the ring junction can now be cis or trans. In 7-substituted-2,3,3a,4,5,7a-hexahydro-1*H*-indenes with a cis-ring junction, catalytic reduction occurs from the expected convex *exo*-face.[12] However, when the ring junction is trans, this together with the extra atom in the tether means that there are no longer any very distinct convex or concave faces and mixtures of diastereoisomeric products occur in the carbocyclic series.[13] However, with indolizidines there are examples where hydrogenation occurs preferentially from the unexpected *endo*-face.[14]

Table 1. Reducing agent and conditions

Reducing agent	Conditions	Ratio **3**:**4**
PtO_2 5 mol %	1 atm H_2, MeOH, rt, 48 h	1.8:1
10% Pd/C, 5 mol %	1 atm H_2, MeOH, rt, 65 h	1.9:1
5% Pt/C, 5 mol %	1 atm H_2, MeOH, rt, 65 h	3.6:1
5% Rh/alumina	1 atm H_2, MeOH, rt, 16 h	No reaction
$RhCl(PPh_3)_3$, 5 mol %	1 atm H_2, C_6H_6, rt, 17 h	No reaction
Diimide	H_2O_2/N_2H_2	15:1

Global energy minimisation (MM2 CS Chem3D Pro) indicates that dehydroindolizidinone **2** is fairly flat (Fig. 2). On steric grounds alone there should be little discrimination between the *exo*- and *endo*-faces. One possible explanation for the selectivity on the diimide reduction, which is an electrophilic process, is that there is a stereoelectronic Cieplak effect[15] which is directing the hydrogenation to the face opposite the 'donating' axial H8a and H6 protons. The Cieplak stereoelectronic effect has previously been invoked to explain the stereochemical outcome of hydrogenations using diimide,[16] and is commonly employed to explain curious selectivities in both nucleophilic and electrophilic additions to dehydroindolizidines.[17] It should be noted that although Cieplak's rationalisation is very popular amongst organic chemists it has gained less favour with theoretical chemists.[18]

It is not clear at present why diimide reduction gives the best selectivity. It is generally accepted that there is a lack of correlation between the stereochemistries of catalytic and diimide reduction of alkenes.[19] The problem with metal catalysts is that these can isomerise alkenes prior to reduction which complicates matters. It cannot be ruled out that compound **3** is the product of a double bond isomerisation prior to reduction and that it is the relative rates of isomerisation, reduction of a disubstituted, verses trisubstituted double bond, which dictates the stereochemical outcome. This goes some way to rationalising why the stereoselectivity of the catalytic reduction shows variation with catalyst.

In conclusion, we have demonstrated that alkene **1** is a versatile precursor to the heterocyclic core of deoxypumiliotoxin 251H.

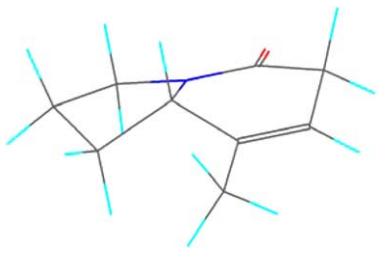

Figure 2. Energy minimised structure of dehydroindolizidinone **2** depicting how flat the structure is. The axial hydrogens on C8a and C6 are perfectly aligned to interact with the σ* orbital of the newly forming carbon hydrogen bond.

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References and notes

1. Lalonde, R. T.; Muhammad, N.; Wong, C. F.; Sturiale, E. R. *J. Org. Chem.* **1980**, *45*, 3664–3671.
2. Aube, J.; Rafferty, P. S.; Milligan, G. L. *Heterocycles* **1993**, *35*, 1141–1147.
3. (a) Satake, A.; Shimizu, I. *Tetrahedron: Asymmetry* **1993**, *4*, 1405–1408; (b) Song, Y.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **2002**, *43*, 8635–8637.
4. Daly, J.; Myers, C. *Science* **1967**, *156*, 970–973.
5. Daly, J.; Garraffo, H.; Spande, T. Amphibian Alkaloids—Chapter 3. In *The Alkaloids*; Cordell, G., Ed.; Academic Press: New York, 1993; Vol. 43, p 185.
6. Jain, P.; Garraffo, H. M.; Spande, T. F.; Yeh, H. J. C.; Daly, J. W. *J. Nat. Prod.* **1995**, *58*, 100–104.
7. Fox, D. N. A.; Lathbury, D.; Mahon, M. F.; Molloy, K. C.; Gallagher, T. *J. Am. Chem. Soc.* **1991**, *113*, 2652–2656.
8. Armstrong, P.; O'Mahony, G.; Nieuwenhuyzen, M.; Stevenson, P. J. *J. Org. Chem.* **2004**, *69*, 3968–3971.
9. Corey, E. J.; Mock, W. L.; Pasto, D. J. *Tetrahedron Lett.* **1961**, *2*, 347–352.
10. Donohoe, T. J.; Guillermin, J. B.; Walter, D. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1369–1375; Hudlicky, T.; Sinaizingde, G.; Seoane, G. *Synth. Commun.* **1987**, *17*, 1155–1163; Niwa, H.; Ishiwata, H.; Kuroda, A.; Yamada, K. *Chem. Lett.* **1983**, 789–790; Roche, C.; Delair, P.; Greene, A. E. *Org. Lett.* **2003**, *5*, 1741–1744; Andersson, P. G.; Backvall, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 8696–8698.
11. Whitesell, J. K.; Matthews, R. S. *J. Org. Chem.* **1977**, *42*, 3878–3882; Paquette, L. A.; Galemmo, R. A.; Caille, J. C.; Valpey, R. S. *J. Org. Chem.* **1986**, *51*, 686–695.
12. Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 2945–2948.
13. Mehta, G.; Reddy, D. S. *Synlett* **1997**, 612–615.
14. Choi, J. K.; Hart, D. J.; Tsai, Y. M. *Tetrahedron Lett.* **1982**, *23*, 4765–4768; Choi, J. K.; Hart, D. J. *Tetrahedron* **1985**, *41*, 3959–3971; Ohta, A.; Takahashi, N.; Shirokoma, Y.; Yuasa, K.; Kurihara, T.; Miyamae, H. *Heterocycles* **1990**, *30*, 875–884; Harris, J. M.; Padwa, A. *J. Org. Chem.* **2003**, *68*, 4373–4381.
15. Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540; Cieplak, A. S. *Chem. Rev.* **1999**, *99*, 1265–1336.
16. Hudec, J.; Huke, J.; Liebeschuetz, J. W. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1129–1138.
17. Toyooka, N.; Fukutome, A.; Shinoda, H.; Nemoto, H. *Tetrahedron* **2004**, *60*, 6197–6216; Toyooka, N.; Nemoto, H.; Kawasaki, M.; Garraffo, H. M.; Spande, T. F.; Daly, J. W. *Tetrahedron* **2005**, *61*, 1187–1198; Hanessian, S.; Sailes, H.; Munro, A.; Therrien, E. *J. Org. Chem.* **2003**, *68*, 7219–7233.
18. Dannnenberg, J. J. *Chem. Rev.* **1999**, *99*, 1225–1241.
19. Siegel, S.; Foreman, M. G.; Johnson, D. *J. Org. Chem.* **1975**, *40*, 3589–3593.