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Expedient synthesis of (+)-*trans*-5-allylhexahydroindolizidin-3-one

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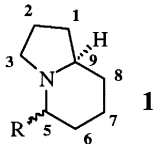
Abstract

Treatment of the bicyclic iminium ion derived from 5-methoxyhexahydroindolizidin-3-one with allyltrimethylsilane gave exclusively the diastereoisomer in which the allyl group was axial. This substrate is a useful precursor to 5-propyl-3-alkylindolizidine alkaloids. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: *N*-acyliminium ion; indolizidine; pyroglutamate; 1,3-allylic strain.

5-Alkyl- and 3,5-dialkylindolizidines are common secondary metabolites, usually isolated from the skins of Dendrobatid frogs or ant venoms.[1] These compounds display a range of biological activities, the most notable being the ability to block nicotinic receptor channels.[2]

A large number of strategies exist for the synthesis of both *cis*- and *trans*-5-substituted indolizidines **1**, and the stereoselectivities for the various bond forming processes are summarised in Table 1 (entries 1–6). Reactions involving sp^2 hybridised functional groups, under thermodynamic control, generally give *cis*-indolizidines **1**, reflecting the greater stability of this isomer.



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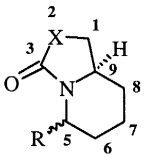

2a X=CH$_2$
2b X=O

The situation changes dramatically when a carbonyl group is present at C3 in the indolizidine **2a** or 2-oxaindolizidine **2b**, and the stereoselectivities for the various bond forming processes are summarised in Table 1 (entries 7–12). It is immediately apparent that there is a strong preference for the *trans*-indolizidines in reactions in which a new chiral centre is produced. It is well documented that the preference for a 2-substituent in *N*-acyl 2-piperidines is axial.[17] This arises due to partial double bond character in the amide linkage giving rise to pseudo 1,3-allylic strain with the 2-equatorial substituent.[18] This interaction is usually larger than the corresponding 2,4 or 2,6-diaxial interactions. It is likely that

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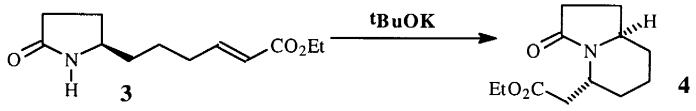
Table 1

Entry	Product	Bond formed	Stereochemistry
1	**1**	R-C5	*Cis* or *trans*[3]
2	**1**	N-C5	Usually *cis*.[4] Only *trans* when C5 is chiral.[5]
3	**1**	N-C3	*Cis* or *trans* stereochemistry determined by piperidine.[6]
4	**1**	C5-C6	*Cis*[7]
5	**1**	C1-C9	*Trans*[8]
6	**1**	C8-C9	No examples found.
7	**2b**	R-C5	*Trans*[9]
8	**2a**	N-C5	*Trans*[10] or *cis*[11]
9	**2a**	N-C3	*Cis* or *trans* stereochemistry determined by piperidine.[12]
10	**2a**	C5-C6	*Trans*[13] or *cis*[14]
11	**2a/2b**	C1-C9	*Trans*[15]
12	**2a/2b**	C8-C9	*Trans*[16]

this effect is also being observed in the indolizidines **2a** and **2b**, where the carbonyl group is forcing the 5-substituent axial, hence favouring the transition state leading to the *trans*-diastereoisomers. Hart was the first to use this concept to control relative stereochemistry in 5-substituted indolizidines.[16]

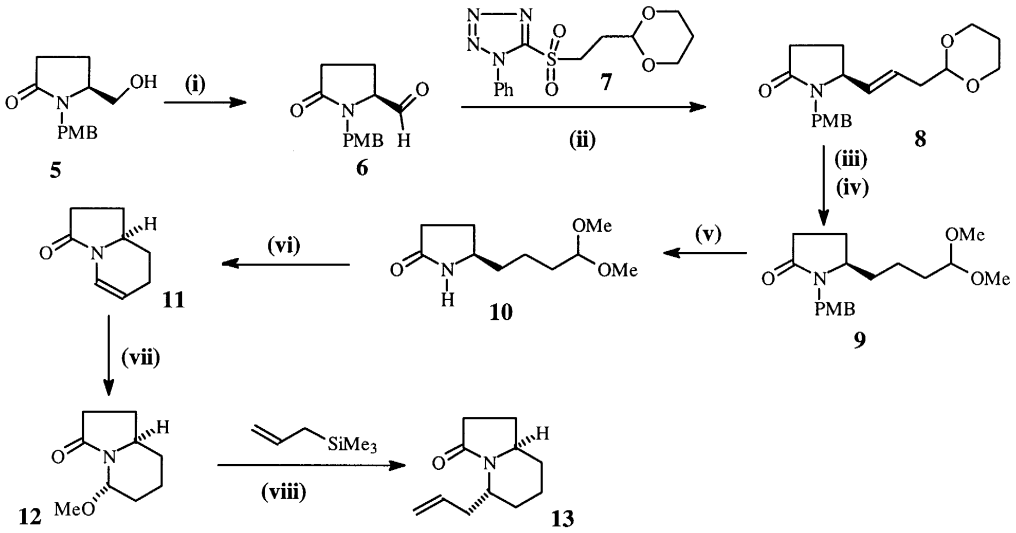
Recently we have been developing new routes to 5-substituted indolizidines using pyroglutamates as chiral precursors.[10a] The advantage of this approach is that the protected pyroglutamates are readily available in both enantiomeric forms, and the carbonyl group at C3 is a convenient functionality for introducing an additional alkyl group at that position. Hence, when acrylate **3** was treated with a catalytic quantity of potassium *t*-butoxide it cyclised and gave exclusively the *trans*-diastereoisomer **4** with the pendent alkyl group axial (Scheme 1). However, the synthesis of acrylate precursor **3** required eleven synthetic steps from known *N*-(*p*-methoxybenzyl)pyroglutamic acid, making this approach unattractive.



Scheme 1.

We now report a more direct route to *trans*-5-allylhexahydroindolizidines based on *N*-acyl iminium chemistry[19] (Scheme 2). Alcohol **5** is readily available, in large quantity, from *S*-glutamic acid by Kobayashi's method[20] and was the starting point for this investigation. Three carbon extension of the side chain was accomplished in 53% overall yield from **5** by a modified Julia reaction of sulphone **7** with aldehyde **6**. Although aldehyde **6** is too unstable to chromatograph, it can be stored for days at −5°C with no detectable racemisation. This was confirmed by reduction to the alcohol followed by proton NMR analysis of corresponding MTPA esters. Modified Julia reaction, using Julia's original sulphone,[21] gave none of the desired alkene **8**. However, with the sulphone derived from phenyl-1*H*-tetrazole-5-thiol, Kocienski's modification,[22] workable yields of the *E*-alkene **8** were reproducibly obtained. As expected, no *Z*-isomer was detected in the crude reaction mixture. Reduction of the alkene followed by *trans*-acetalisation gave the dimethylacetal **9** in 91% for the two steps. It was envisaged that oxidative removal of the *p*-methoxybenzyl group using ceric ammonium nitrate would lead directly to *N,O*-acetal **12**, since nitric acid, a product of the oxidation should catalyse the cyclisation. However, this only led to intractable material and a less desirable three step procedure was adopted. Reductive removal of the *p*-methoxybenzyl group using sodium in liquid ammonia gave **10** in 65% yield. This substrate also proved remarkably resistant to forming *N,O*-acetal **12**, only giving cyclic enamide **11** in a poor 41%

yield when treated with dilute hydrochloric acid. However, this cyclic enamide could be converted into **12** (68% yield, axial isomer), by treating it with camphorsulphonic acid in methanol. Treatment of **12** with titanium tetrachloride and allytrimethylsilane gave the allylated adduct **13** in 70% yield, and in diastereoisomerically pure form.



Scheme 2. Reagents: (i) Dess–Martin periodinane. (ii) DME $KN(SiMe_3)_2$. (iii) H_2, PtO. (iv) HCl, MeOH. (v) Na/NH_3/EtOH. (vi) HCl, H_2O, THF. (vii) Camphorsulphonic acid, MeOH. (viii) $TiCl_4$ CH_2Cl_2 −30°C

The relative stereochemistry of indolizidine **13** was established by proton NMR spectroscopy.[23] Protons H5 and H9 had very different chemical shifts δ 4.30 and 3.55, respectively, with multiplicities qd J 6.5, 1.2 Hz and dtd J 11.2, 7.4, 3.6 Hz. The large coupling constant to H9, 11.2 Hz, confirmed that this atom was axial. Since the largest coupling constant to H5 was only 6.5 Hz this strongly suggested that this atom was equatorial. Comparison of the proton NMR spectra of indolizidinone **13** with the known *cis*-[24] and *trans*-5-propylindolizidinones[25] confirmed the stereochemical assignment was *trans*. In particular the proton NMR signals for H5 and H9 in the *cis*-isomer coincided at δ 3.2 whereas in the *trans*-isomer these signals appeared as discreet multiplets at δ 4.08 and 3.7, respectively.

In conclusion, we have developed a short route to 5-allylhexahydroindolizidin-3-ones, in eight steps from a known alcohol **5**, allowing rapid access to chiral 5-propyl-3-alkylindolizidine alkaloids.[26]

Acknowledgements

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23. $[\alpha]_D$=+35.5 (*c*=5.4, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 5.77 (1H, ddt J 17.1, 10.1, 7.1, C*H*=CH_2), 5.10–5.01 (2×1H, 2×m, CH=CH_2), 4.30 (1H, qd, J 6.5, 1.2Hz, =CHCH_2C*H*N), 3.55 (1H, dtd J 11.2, 7.4, 3.6Hz, NC*H*), 2.38–2.31 (31×H, 3×m, CH_2CO and =CH-C*H*H), 2.24 (1H, m, =CH-CH*H*), 2.16 (1H, dtd, J 12.9, 7.3, 5.4 $COCH_2$C*H*H), 1.85 and 1.15 ($1H_e$, $1H_a$, 2×m, CH_2) 1.69–1.44(5×1H, 5×m). $\delta_{C\text{-}13}$(125 MHz, $CDCl_3$) 174.10(C3), 135.59(=*C*H), 117.38(=*C*H_2), 53.66(C9), 47.71(C5), 35.20(=CH*C*H_2), 34.09(CH_2), 30.78(C3), 27.01(CH_2), 25.98(C2), 19.21(CH_2).
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