Synthesis of *trans*-5-Substituted-indolizidin-3-one

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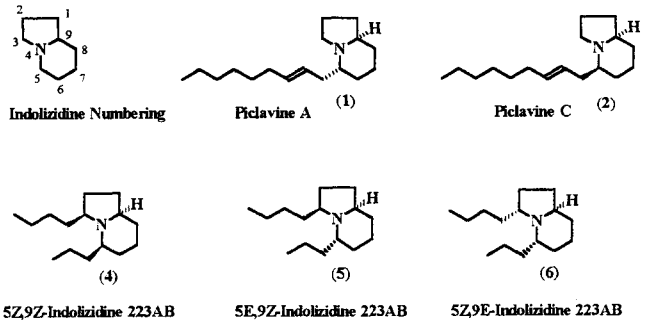
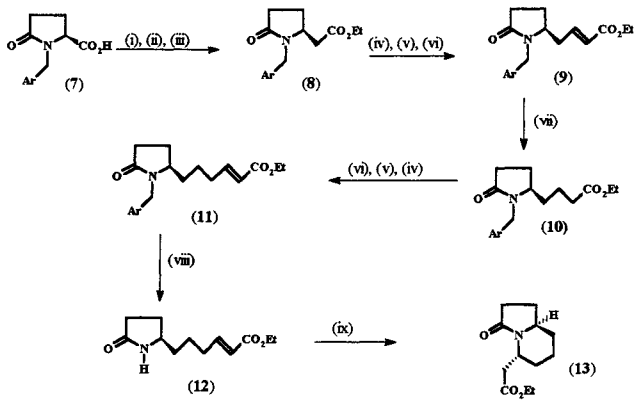
cis and *trans*-5-substituted indolizidines are common structural elements in a number of biologically active, naturally occurring compounds.[1] Piclavines A (**1**) and C (**2**)[2], are indolizidine based anti-bacterial agents isolated from the tunicate *Clavelina picta*. Indolizidine 223AB diastereoisomers (**3-5**) have been identified in the defensive skin secretions of a bufonid toad[3] and are known to block nicotinic receptor channels[4]. There has been intense interest in the stereoselective synthesis of both *cis* and *trans*-2,6-disubstituted alkyl piperidines and the corresponding 5-substituted indolizidines derived from them and a number of elegant methodologies have emerged.[5] To date there are more methods for synthesising 5-*cis*-substituted indolizidines than there are for preparing the corresponding *trans*-isomer. Many of the methods used for preparing the *trans*-isomer can be modified to give the *cis* isomer. This largely reflects the greater thermodynamic stability of the 5-*cis* isomer over the 5-*trans* isomer.



We now report a new route to 9-substituted indolizidin-3-ones which gives exclusively the *trans*-diastereoisomer. The key step is an intramolecular base catalysed 1,4-addition of a pyrrolidin-2-one to an acrylate which places the newly formed pendant group axial.

Scheme 1 outlines the synthesis of the key intermediate (**12**) starting from a suitably protected pyroglutamic acid (**7**), which in turn was readily available from glutamic acid using the literature procedure[6]. One carbon chain extension was achieved in three steps in high overall yield (77%) by converting the corresponding acid chloride to the diazoketone, followed by Wolff rearrangement to give ester (**8**). The remaining four carbon atoms in the side chain were introduced by an iterative procedure, adding two carbons at a time, which involved reduction of ester to primary alcohol followed by oxidation to the aldehyde and Wittig olefination (**Scheme 1** steps(iv-vi)). The only reactions of note in this sequence were the chemoselective sodium borohydride reductions of the two esters, one and three carbons removed from the lactam.[7] Overall yields for these three step sequences were 53% and 58% respectively. Oxidative removal of the p-methoxybenzyl group with ceric ammonium nitrate (CAN) give the key precursor lactam (**12**) in 58% yield. Treatment of (**12**) with 0.5 eq of potassium t-butoxide in THF, -40°-20°C over 12 hours gave the indolizidine (**13**) as a single stereoisomer in 85% yield.

The proton nmr spectrum of indolizidine (**13**) is worthy of comment. Proton H9 δ(3.61, dddd J=11.2, 7.5, 7.5, 3.7Hz) has a wide multiplet bandwidth, 29.9Hz and a chemical shift much as expected. The 11.2 Hz coupling constant indicates that it is axial. Proton H5 δ(4.6, m), has a



Reagents: (i) Thionyl chloride. (ii) Diazomethane. (iii) Silver benzoate, ethanol. (iv) 4 M eq sodium borohydride in ethanol 4 days 25°C. (v) Dess-Martin Periodinane. (vi) Triethylphosphonoacetate, sodium hydride, THF. (vii) Magnesium in ethanol. (viii) Ceric ammonium nitrate water/acetonitrile, (ix) Potasssium t-butoxide, THF, -40-25°C

Scheme 1

narrow multiplet bandwidth 20.2Hz and its anomolously high chemical shift indicates it is in the deshielding cone of the lactam carbonyl group. Due to its complexity and narrowness, all the coupling constants could not be directly extracted from this multiplet. However analysis of the multiplets for the diastereotopic protons adjacent to the ester showed that the coupling to these protons from H5 were 7.9 and 7.6Hz. Therefore these two couplings are making up 15.5Hz of the bandwidth of H5 and the sum of the remaining two coupling constants is 4.7Hz, proving that H5 is equatorial. Further tentative evidence for the stereochemical assignment was that no nOe was observed between H5 and H9 on irradiation of both H5 and H9.

The thermodynamic axial preference for substituents at the 2-position in acyl piperidines is well documented.[8] This arises due to partial double bond character between the nitrogen and the carbonyl group, giving rise to allylic 1,3-strain with the 2-equatorial substituent. This interaction is usually greater than other 2,4-diaxial interactions that may arise due to conformational change[9]. It therefore seems likely that allylic-1,3-strain, via the amide enolate, in the six membered ring transition state is forcing the newly formed ethyl aceto group axial.

Cyclisation (12 → 13). A suspension of potassium t-butoxide (11mg, 0.01mmol) in THF (0.5ml) under nitrogen was cooled to -40°C and amide (**12**, 50mg, 0.22mmol) in dry THF (0.5ml) was added dropwise over 1 minute. The resulting mixture was allowed to warm to room temperature and stirred for 12h. THF was removed under reduced pressure and flash chromatography, solvent ethyl acetate, gave (**13**, 42.5mg, 85%) as a clear oil R_f(ethyl acetate)=0.4. $C_{12}H_{19}NO_3$ requires M^+ 225.13652, found M^+ 225.13649. $[\alpha]_D$ =+78.9 (c=3.3, $CHCl_3$). δ(500MHz) 4.6(1H, m, bandwidth=20.2Hz, NC**H**CH_2CO), 4.04(2H, t, J=7.2Hz, C**H**$_2$O), 3.61(1H, dddd, J=11.2, 7.5, 7.5, 3.7Hz, C**H**N) 2.43(1H, dd, J=7.9, 14.1Hz, CHC**H**HCO_2) 2.23(1H, dd, J=14.1, 7.5Hz CHCH**H**CO_2) 2.21(2x1H, m, overlapping multiplets, NCOC**H**$_2$) 1.6(8H, overlapping multiplets methylene envelope), 1.16(3H, t, J=7.2Hz, C**H**$_3CH_2$). δ(125.8MHz) 173.70, 170.95, 60.73, 53.20, 45.13, 35.34, 33.37, 30.19 27.45, 25.62, 18.64, 14.14.

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