5-*endo-trig* Cyclisations in heterocycle synthesis: enantiospecific synthesis of (+)-monomorine I

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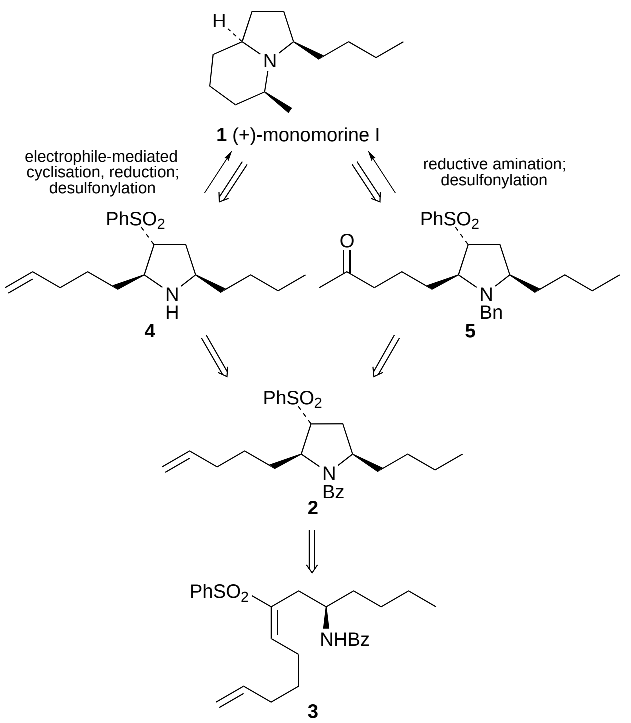
The indolizidine alkaloid monomorine I is synthesised from D-norleucinol using 5-*endo-trig* cyclisation and intramolecular reductive amination as the key ring-forming steps.

Pyrrolidines occur widely in nature as pheromones, venoms and toxins, and as structural motifs in more complex molecules such as pyrrolizidines and indolizidines.[1] As part of our programme investigating 5-*endo-trig* cyclisation reactions[2] for heterocycle construction[3] we have been looking at sulfone-mediated assembly of pyrrolidines, and have discovered that 2,5-disubstituted pyrrolidines may efficiently and stereoselectively be prepared from amino acid-derived precursors.[4] Here we report the application of this methodology to the total synthesis of the indolizidine alkaloid monomorine I **1**, the trail pheromone of the Pharaoh worker ant *Monomorium pharaonis*.[5,6]

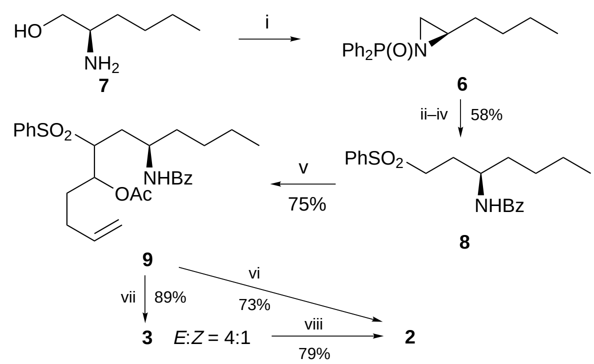
Our synthetic plan for **1** involved initial assembly of the pyrrolidine ring in **2** by 5-*endo-trig* cyclisation reaction of a substrate such as **3**. Closure of the remaining, six-membered cycle would be effected either by electrophile-induced addition of the pyrrolidine nitrogen atom to the distal double bond, as in **4**, or by intramolecular reductive amination of a derived side-chain ketone moiety, as in **5** (Scheme 1).

Retrosynthetic analysis of the cyclisation substrate **3** indicated *N*-protected aziridine **6** as the starting material. This was synthesised in two steps from commercially available D-norleucine;† reduction using the $NaBH_4$–iodine reagent system described by Meyers[7] gave D-norleucinol **7**, which was converted directly into **6** by treatment with diphenylphosphinic chloride and triethylamine in THF followed by excess sodium hydride according to the method of Sweeney (Scheme 2).[8] Addition of **6** to a THF–*N*,*N*,*N*′,*N*′-tetramethylethylenediamine solution of lithio(phenylsulfonyl)methane followed by proton quench gave the expected product of aziridine ring-opening at the less substituted carbon atom. This was dephosphinylated and reprotected as the benzamide **8** in good overall yield for the three steps from **6**.[9] Exposure of **8** to 2 equiv. of base followed by hex-5-enal, and *in situ* trapping of the intermediate alkoxides, gave ester **9**, mostly as one diastereoisomer.‡ Pyrrolidine formation was effected *in a single step* by treating a dilute THF solution of **9** with 2 equiv. of potassium *tert*-butoxide in the presence of *tert*-butyl alcohol, which effected one-pot elimination to give **3** followed by cyclisation. Pyrrolidine **2** formed in this way was a single, 2,5-*syn* diastereoisomer as evidenced by single-crystal X-ray diffraction analysis.§ Interestingly, treatment of **9** with 1 equiv. of base followed by *immediate* proton quench gave in 89% isolated yield a 4:1 *E*:*Z* mixture of geometric isomers of **3**, which could be converted into **2** in a separate operation by treatment with a further 1 equiv. of base. Compound **2** prepared in this way was identical in all respects to material made in the one-pot reaction.

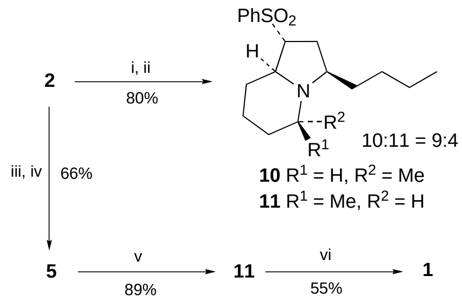
Initial attempts to complete the assembly of the indolizidine nucleus by closure of the six-membered ring involved mercury(II)-assisted cyclisation. Thus, debenzoylation of **2** using Super-Hydride®,[10] and treatment of the resulting free amine with $Hg(OAc)_2$ followed by *in situ* reduction with $NaBH_4$,[11] gave in 90% yield a 9 : 4 mixture of **10** and the desired



Scheme 1



Scheme 2 *Reagents and conditions*: i, $Ph_2P(O)Cl$, (2.1 equiv.), Et_3N (3 equiv.), THF (0.3 M), 0 °C→room temp., 12 h, then excess NaH, room temp., 1–2 weeks; ii, $PhSO_2Me$ (1 equiv.), BuLi (1 equiv.), 3 : 1 THF–$Me_2N(CH_2)_2NMe_2$ (0.4 M), −78 °C, add **6**, −78 °C→room temp., 12 h; iii, $BF_3\cdot OEt_2$ (10 equiv.), 1 : 1 CH_2Cl_2–MeOH (0.1 M), room temp., 12 h; iv, BzCl (1.2 equiv.), pyridine (1.1 equiv.), CH_2Cl_2 (0.2 M), room temp., 12 h, work-up with $Me_2N(CH_2)_3NH_2$; v, BuLi (2.1 equiv.), 3 : 1 THF–$Me_2N(CH_2)_2NMe_2$, −78 °C, add hex-5-enal (1.3 equiv.), −78 °C, 40 min, then add Ac_2O (5 equiv.), −78 °C→room temp., 12 h; vi, Bu^tOK (2.1 equiv. of a 1 M solution in THF), Bu^tOH (10 equiv.) in THF (0.033 M), room temp., 12 h; vii, Bu^tOK (1.05 equiv. of a 1 M solution in THF), Bu^tOH (5 equiv.) in THF (0.1 M), room temp., < 1 min; viii, Bu^tOK (1.05 equiv. of a 1 M solution in THF), Bu^tOH (10 equiv.) in THF (0.033 M), room temp., 12 h



Scheme 3 *Reagents and conditions*: i, $LiBHEt_3$ (2.2 equiv.), THF (0.23 M), room temp., 8 h; ii, $Hg(OAc)_2$ (1.05 equiv.), 1 : 1 THF–H_2O (0.25 M), then $NaBH_4$–NaOH (0.75 equiv.); iii, DIBAL-H (4 equiv.), CH_2Cl_2 (0.1 M), −78 °C→room temp., 2 h; iv, $Hg(OAc)_2$ (1.05 equiv.), 3 : 1 THF–H_2O (0.2 M), room temp., 1 h, then add to $PdCl_2$ (0.6 equiv.), $CuCl_2$ (3 equiv.), THF (0.2 M), room temp., 1.5 h; v, 10% Pd(C), cyclohexa-1,4-diene (15 equiv.), MeOH (0.1 M), reflux, 4 h; vi, $Na^+C_{10}H_8^-$ (3.5 equiv.), THF (0.05 M), room temp., 5 min

C-2 epimer **11**. The stereochemical assignment of **11**, and therefore that of **10** followed from the nuclear Overhauser enhancements of the signals corresponding to the α-hydrogen atoms at C-6 and C-9 observed on irradiation of the C-2 methyl group. In view of this adverse selectivity, the reductive amination route was pursued. Partial reduction of **2** to the *N*-benzyl analogue using DIBAL-H, and oxidation of the side-chain double bond in the product using a modified Wacker procedure[12] gave ketone **5**. This was subjected to catalytic transfer hydrogenation,[13] which effected sequential hydrogenolytic debenzylation and intramolecular reductive amination[14] to give exclusively **11**, which was identical in all respects to material prepared *via* the mercury-mediated cyclisation route. Finally, *brief* exposure¶ of **11** to sodium naphthalenide in THF followed by NH_4Cl work-up gave (+)-monomorine I **1** (Scheme 3), which showed ^1H and ^{13}C NMR, IR and mass spectral and optical rotation characteristics in agreement with published values.[6]

In summary, the synthesis of (+)-monomorine I has been achieved in nine steps from aziridine **6**, which is available in two steps by known methods from D-norleucine. Both ring-forming steps are highly stereoselective, and our synthesis compares favourably with published approaches.[6] The complete selectivity of the pyrrolidine-forming reaction is particularly notable, and should be applicable to the synthesis of other pyrrolidine-containing alkaloids, and related pyrrolizidines and indolizidines.

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Footnotes and References

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† All yields reported herein refer to isolated, pure materials which had ^1H and ^{13}C NMR, IR and high-resolution mass spectral characteristics in accord with the proposed structures.

‡ We have not been able to assign the configurations of the phenylsulfonyl- and acetoxy-substituted stereocentres.

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¶ Work-up after no more than 5 min was crucial to the success of this reaction. We thank Mr Simon Ward (University of Cambridge) for informing us of the importance of short reaction times in these transformations.

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