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

Malcolm B. Berry,[a] Donald Craig,*[a] Philip S. Jones[b] and Gareth J. Rowlands[a]

[a] *Department of Chemistry, Imperial College of Science, Technology and Medicine, London, UK SW7 2AY*
[b] *Roche Discovery Welwyn, Broadwater Road, Welwyn Garden City, Hertfordshire, UK AL7 3AY*

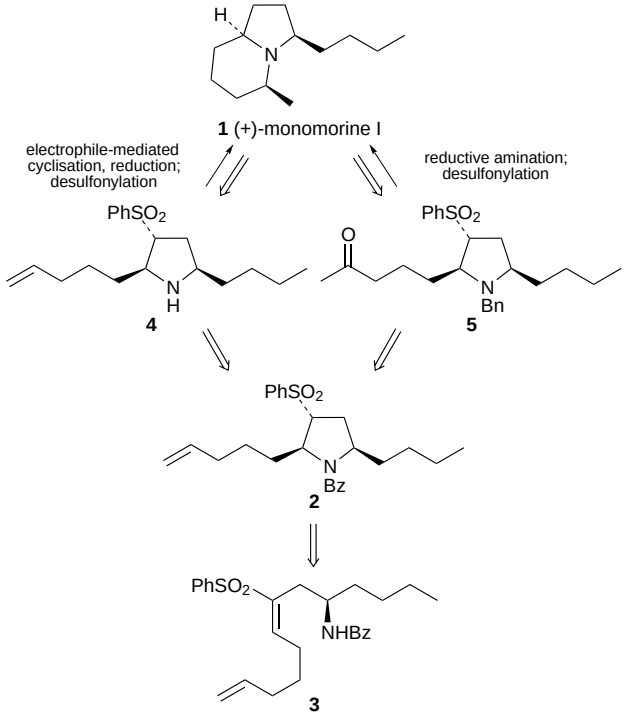
The indolizidine alkaloid monomorine I is synthesised from D-norleucinol using 5-*endo-trig* cyclisation and intramolecular reductive amination as the key ring-forming steps.

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]

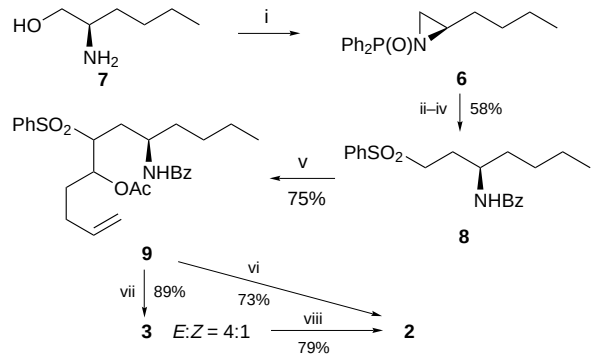
Our synthetic plan for **1** involved initial assembly of the pyrrolidine ring in **2** by 5-*endo-trig* cyclisation reaction of a substrate such as **3**. Closure of the remaining, six-membered cycle would be effected either by electrophile-induced addition of the pyrrolidine nitrogen atom to the distal 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.

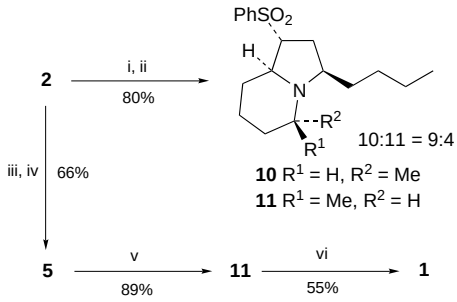
Initial attempts to complete the assembly of the indolizidine nucleus by closure of the six-membered ring involved mercury(II)-assisted cyclisation. Thus, debenzoylation of **2** using Super-Hydride®,[10] and treatment of the resulting free amine with $Hg(OAc)_2$ followed by *in situ* reduction with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

We thank the SERC/EPSRC (CASE Studentships to M. B. B. and G. J. R) and Roche Discovery Welwyn for financial support of this research.

Footnotes and References

* E-mail: dcraig@ic.ac.uk

† 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.

§ We thank Professor David J. Williams and Dr Andrew J. P. White of this Department for this determination.

¶ 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.

1 For reviews, see A. R. Pinder, *Nat. Prod. Rep.*, 1992, **9**, 17; J. P. Michael, *Nat. Prod. Rep.*, 1994, **11**, 17.
2 J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 734.
3 D. Craig and A. M. Smith, *Tetrahedron Lett.*, 1992, **33**, 695; D. Craig, N. J. Ikin, N. Mathews and A. M. Smith, *Tetrahedron Lett.*, 1995, **36**, 7531. For other pyrrolidine-forming 5-*endo-trig* cyclisation reactions, see P. Knochel and J. F. Normant, *Tetrahedron Lett.*, 1985, **26**, 4455; A. Padwa and B. H. Norman, *J. Org. Chem.*, 1990, **55**, 4801.
4 M. B. Berry, Ph.D. thesis, University of London, 1993; G. J. Rowlands, Ph.D. thesis, University of London, 1996.
5 Isolation and characterisation: F. J. Ritter, I. E. M. Rotgans, E. Talman, P. E. J. Verwiel and F. Stein, *Experientia*, 1973, **29**, 530.
6 For a comprehensive collection of references to published syntheses of both racemic and enantiomerically pure monomorine I, see M. J. Munchhof and A. I. Meyers, *J. Am. Chem. Soc.*, 1995, **117**, 5399.
7 M. J. McKennon and A. I. Meyers, *J. Org. Chem.*, 1993, **58**, 3568.
8 H. M. I. Osborn, J. B. Sweeney and W. Howson, *Synlett*, 1994, 145.
9 We did not investigate reactions of lithio(phenylsulfonyl)methane with *N*-benzoylaziridines, in light of an account describing their non-chemoselective reaction with certain carbon nucleophiles: J. E. Baldwin, R. M. Adlington and N. G. Robinson, *J. Chem. Soc., Chem. Commun.*, 1987, 153.
10 H. C. Brown and S. C. Kim, *Synthesis*, 1977, 635.
11 J. J. Perie, J. P. Laval, J. Roussel and A. Lattes, *Tetrahedron*, 1972, **28**, 675.
12 G. T. Rodeheaver and D. T. Hunt, *J. Chem. Soc., Chem. Commun.*, 1971, 818.
13 A. M. Felix, E. P. Heimer, T. J. Lambros, C. Tzougraki and J. Meienhofer, *J. Org. Chem.*, 1978, **43**, 4194.
14 R. V. Stevens and A. W. M. Lee, *J. Chem. Soc., Chem. Commun.*, 1982, 102.

Received in Liverpool, UK, 29th August 1997; 7/06333D