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Stereocontrolled approach to 1-azabicyclo[4.1.0]heptanes: application to the synthesis of *trans*-2,6-disubstituted piperidines

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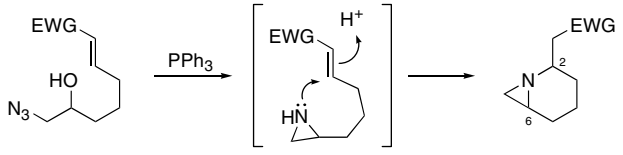
Abstract—Stereocontrolled synthesis of a 1-azabicyclo[4.1.0]heptane is achieved by formation of an NH aziridine from the corresponding 1,2-azido alcohol and subsequent intramolecular conjugate addition onto a tethered α,β-unsaturated ester. Regioselective ring opening of the product at C-7 by heteroatom based nucleophiles yields *trans*-2,6-disubstituted piperidines in moderate to good yields.

Relief of ring strain provides a strong thermodynamic driving force for many important chemical reactions. For example, the chemistry of epoxides and aziridines, highly valued intermediates in organic synthesis, is dominated by their ring opening reactions.[1,2] Strained polycycles containing the aziridine nucleus are also useful in medicinal and synthetic chemistry. For example, the 1-azabicyclo[4.1.0]heptane (1-ABH) ring system has been used to produce DNA targeting agents,[3] as well as potential enzyme inhibitors of chorismate mutase,[4] and various glycosidases.[5] Moreover, strained 1-ABHs have been used as intermediates en route to several alkaloids including aspidospermidine,[6] vindoline[7] and cryptopleurine.[8]

A number of methods exist for the synthesis of 1-ABHs. Most commonly, these involve ring closure reactions of preformed piperidines,[3,5,9] cycloamination of aziridine-containing olefins,[10] Diels–Alder reactions of 2*H*-azirines with dienes,[11] or dipolar cycloaddition of azides onto olefins with subsequent extrusion of molecular nitrogen.[6–8] However, in view of the usefulness of the 1-ABH nucleus, the development of new approaches to this ring system are merited. In this Letter, we describe a simple, stereocontrolled approach to 1-ABHs based upon a 'one-pot' double cyclisation sequence. Moreover, we demonstrate that the resulting 1-ABHs can be used to prepare a range of highly functionalised *trans*-2,6-disubstituted piperidines by regiospecific opening of the resultant aziridine ring.

Our strategy for the construction of 1-ABHs is illustrated in Scheme 1. Reaction of a 1,2-azido alcohol with a phosphine was expected to trigger Staudinger-type closure[12] to the corresponding NH aziridine. Further intramolecular conjugate addition of this aziridine onto a tethered alkene bearing an electron withdrawing group (EWG) was anticipated to lead to the 1-ABH in a single operation.[13] From the outset of this work, it was apparent that control of the relative stereochemistry at C-2 and C-6 would be essential if this method was to have significant utility.

To test these ideas, we targeted the synthesis of 1-azabicyclo[4.1.0]heptane **1** incorporating an α-amino ester side-chain. The synthesis of the requisite 1,2-azido alcohol precursor was achieved in just three steps from commercially available methyl 2-benzyloxycarbonylamino-2-(dimethoxy-phosphinyl)acetate (**2**) (Scheme 2). Treatment of **2** with 5-hexenal[14] in the presence of DBN provided dehydroamino ester **3** in 79% yield as a



Scheme 1. Proposed double cyclisation route to substituted 1-ABHs.

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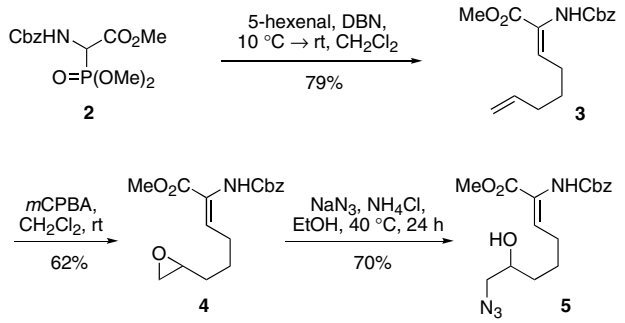
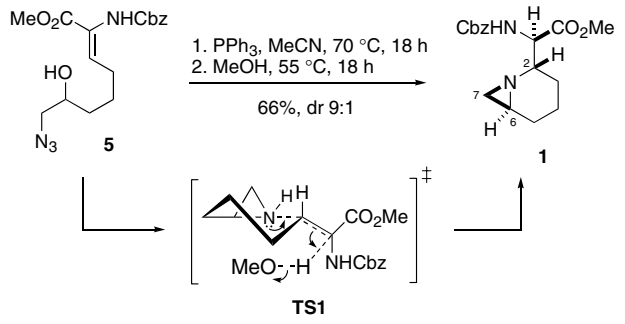


Scheme 2. Synthesis of 1,2-azido alcohol **5**.

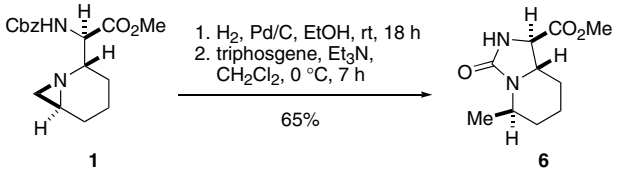
single geometric isomer after column chromatography. The (*Z*)-stereochemistry of the trisubstituted double bond was assigned by analogy with closely related systems.[13,15] Chemoselective epoxidation of the more nucleophilic double bond of **3** was achieved using *m*CPBA, which provided monoepoxide **4** in 62% yield. Subsequent ring opening of this epoxide with sodium azide furnished azido alcohol **5** as a single regioisomer in 70% yield.

With 1,2-azido alcohol **5** in hand, the double cyclisation could be examined. This azide was treated under Staudinger-type conditions with triphenylphosphine to produce the corresponding NH aziridine.[16] Conjugate addition of this aziridine to the α,β-unsaturated ester to assemble the 1-ABH did not proceed in MeCN. However, by simply removing the solvent and redissolving the NH aziridine in MeOH, the second cyclisation to 1-azabicyclo[4.1.0]heptane **1** could be achieved (Scheme 3). Of the four possible diastereomers that could be produced, only two compounds were detected in appreciable amounts in the crude ^{1}H NMR. After column chromatography, **1** was isolated as a 9:1 mixture of two diastereomers in 66% yield. The stereochemistry of the depicted major diastereomer being deduced by NOE studies[17] and further derivatisation (vide infra). We have been unable to establish if the minor diastereomer is epimeric at C-2, or the α-amino ester centre.

Hydrogenation of **1** using Pd/C resulted in reductive cleavage of the N1–C7 bond of the aziridine ring and concomitant hydrogenolysis of the Cbz group (Scheme 4). Further reaction of the resultant diamine with triphosgene produced crystalline urea **6** as a single



Scheme 3. Stereoselective cyclisation to 1-ABH **1**.



Scheme 4. Derivatisation of 1-azabicyclo[4.1.0]heptane **1**.

diastereoisomer in 65% yield over the two steps. X-ray diffraction performed on a single crystal of **6** grown from diethyl ether confirmed the structure and stereochemistry of this material (Fig. 1). By extrapolation, we conclude that the major diastereomer of **1**, produced by cyclisation of azide **5**, has the stereochemistry illustrated.

The stereochemical outcome of the cyclisation can be rationalised using the transition state **TS1** in which the developing 6-membered ring adopts a half-chair conformation with the alkene placed *pseudo*-equatorial.[19] Concomitant protonation at the α-carbon of the amino ester on the opposite face of the olefin to the incoming aziridine accounts for the observed stereochemical outcome. The need to conduct the cyclisation in a protic solvent is consistent with this assertion. Moreover, high levels of deuterium incorporation at the α-carbon of the amino ester (>80% D) was observed when CD_3OD was used as the cyclisation solvent.

Finally, we have explored the ring opening reactions of **1** with a range of simple nucleophiles (Scheme 5). As anticipated, opening at the more sterically accessible C-7 carbon of the aziridine ring was observed in all cases.[3,5] Using this chemistry, a series of highly functionalised *trans*-2,6-disubstituted piperidines, namely **7**–**9**, were produced in moderate to good yields.

In summary, a new stereocontrolled approach to 1-azabicyclo[4.1.0]heptanes has been devised based upon a simple, double cyclisation sequence. Our initial findings suggest that further ring opening reactions of these

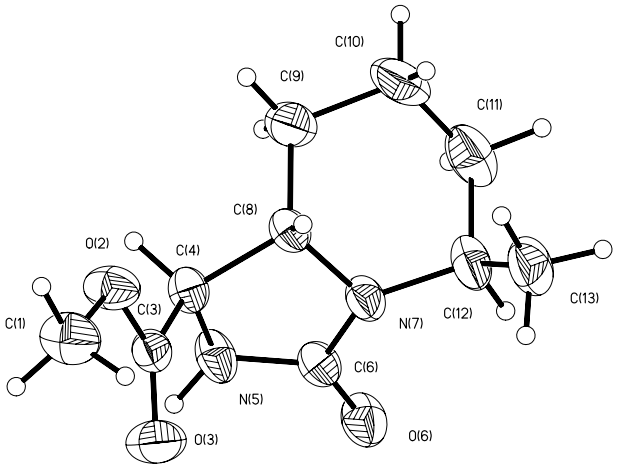
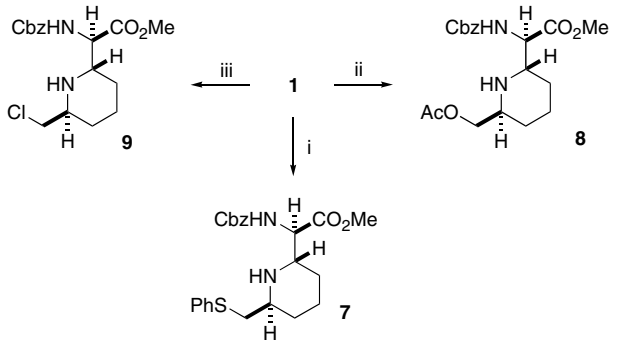


Figure 1. Solid state X-ray crystal structure of urea **6** drawn with thermal ellipsoids at 50% probability.[18]



Scheme 5. Reagents and conditions: (i) PhSH, Et_3N, CH_2Cl_2, 18 h, 67%; (ii) AcOH, CH_2Cl_2, 18 h, 44%; (iii) HCl, MeOH, 18 h, 82%.

systems by heteroatom based nucleophiles provides a flexible approach to a wide variety of functionalised *trans*-2,6-disubstituted piperidines.[20] Work to develop and exploit these findings is ongoing in our laboratories.

Acknowledgments

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Supplementary data

A supplementary data section is provided, which includes experimental procedures and characterisation data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.077.

References and notes

1. For a monograph, see: *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006.
2. For recent reviews, see: Olsen, C. A.; Franzyk, H.; Jaroszewski, J. W. *Eur. J. Org. Chem.* **2007**, 1717–1724; Hu, X. E. *Tetrahedron* **2004**, *60*, 2701–2743; Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247–258; McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347–1365.
3. Hodgkinson, T. J.; Kelland, L. R.; Shipman, M.; Vile, J. *Tetrahedron* **1998**, *54*, 6029–6034.
4. Hediger, M. E. *Bioorg. Med. Chem.* **2004**, *12*, 4995–5010.
5. Goujon, J.-Y.; Gueyrard, D.; Compain, P.; Martin, O. R.; Ikeda, K.; Kato, A.; Asano, N. *Bioorg. Med. Chem.* **2005**, *13*, 2313–2324.
6. Banwell, M. G.; Lupton, D. W.; Willis, A. C. *Aust. J. Chem.* **2005**, *58*, 722–737.
7. Guo, Z. H.; Schultz, A. G. *Tetrahedron Lett.* **2004**, *45*, 919–921.
8. Kim, S.; Lee, Y. M.; Lee, J.; Lee, T.; Fu, Y.; Song, Y.; Cho, J.; Kim, D. *J. Org. Chem.* **2007**, *72*, 4886–4891.
9. Wu, X.; Toppet, S.; Compernolle, F.; Hoornaert, G. J. *Tetrahedron* **2003**, *59*, 1483–1491.
10. Chen, G.; Sasaki, M.; Li, X.; Yudin, A. K. *J. Org. Chem.* **2006**, *71*, 6067–6073.
11. For recent examples, see: Alves, M. J.; Fortes, A. G.; Lemos, A.; Martins, C. *Synthesis* **2005**, 555–558; Timen, A. S.; Somfai, P. *J. Org. Chem.* **2003**, *68*, 9958–9963; Davis, F. A.; Wu, Y.; Yan, H.; Prasad, K. R.; McCoull, W. *Org. Lett.* **2002**, *4*, 655–658.
12. Ittah, Y.; Sasson, Y.; Shahak, I.; Tsaroom, S.; Blum, J. *J. Org. Chem.* **1978**, *43*, 4271–4273.
13. The synthesis of the 1-azabicyclo[3.1.0]hexane skeleton of ficellomycin has been achieved using a related approach, see: Paumier, D.; Garcia, M.; Shipman, M.; Muir, J. C. *Synlett* **2004**, 2212–2214.
14. Prepared by oxidation of 5-hexen-1-ol (PCC, CH_2Cl_2, 18 h, rt), and used directly in the olefination reaction without purification. For full details, see Supplementary data.
15. Hiebl, J.; Kollmann, H.; Rovenszky, F.; Winkler, K. *J. Org. Chem.* **1999**, *64*, 1947–1952.
16. The crude NH aziridine was partially characterised (^{1}H NMR and LRMS). However, attempts to purify it by column chromatography on silica resulted in cyclisation to **1**.
17. The (2*S**,6*S**)-stereochemistry of **1** was deduced by NOE measurements (500 MHz, $CDCl_3$). Specifically, strong reciprocal enhancements were seen between H-2 and H-7 [H-2→H-7: 3.8%; H-7→H–2: 4.4%]. Irradiation of H-7′ produced enhancements of H-6 (1.7%) and H-7 (9.7%). No NOEs between H-2 and H-6 were observed. These observations confirm a *syn*-relationship between the aziridine ring and H-2.
18. Crystallographic data (excluding structure factors) for **6** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 658615. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 0 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
19. For cyclisations involving simple ω-amino alkenes. See, for example, Banwell, M. G.; Bissett, B. D.; Bui, C. T.; Pham, H. T. T.; Simpson, G. W. *Aust. J. Chem.* **1998**, *51*, 9–18; Knapp, S.; Hale, J. J. *J. Org. Chem.* **1993**, *58*, 2650–2651; Knouzi, N.; Vaultier, M.; Toupet, L.; Carrie, R. *Tetrahedron Lett.* **1987**, *28*, 1757–1760.
20. For a review, see: Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781–1813.