Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 2392

www.rsc.org/obc

COMMUNICATION

Furanyl cyclic amines: a diastereoselective synthesis of 2,6-*syn*-disubstituted piperidines under thermodynamic control†‡

Matthew O'Brien,*[a] Andrew Leach,[a] Roly J. Armstrong,[a] Keting Chong[a] and Ross Sheridan[b]

Received 29th November 2011, Accepted 6th January 2012
DOI: 10.1039/c2ob07008a

Utilising the propensity of the 2-furanyl group to facilitate equilibration of an adjacent tosylamide chiral centre, a diastereoselective route to 2,6-*syn*-piperidines was developed that proceeds with high levels of thermodynamic stereocontrol. X-ray crystallography structures suggest that, as seen in similar systems, pseudo-allylic strain between the *N*-tosyl group and the substituents at the 2 and 6 positions dominates stereochemical preference, overriding 1,3 diaxial interactions.

The 2,6-*syn*-piperidine moiety is seen in numerous natural products of biological and pharmacological significance. Examples (shown in Fig. 1) include (−)-lobeline,[1] piclavine A3,[2] *cis*-solenopsin A[3] and (−)-pinidine.[4]

We have recently utilised the ability of the 2-furyl group to facilitate acid catalysed epimerisation at an adjacent ether chiral centre[5] in diastereoselective syntheses of doubly anomeric 6,6-spiroketals[6] (and thence 1,9-*anti*-diols[7]) and 2,6-*syn*-disubstituted tetrahydropyrans.[8] We sought to extend this approach to the synthesis of nitrogen heterocycles, working initially towards 2,6-disubstituted piperidines.[9] Whilst the thermodynamic preference with 2,6-disubstituted tetrahydropyrans is for a *syn* configuration with the two ring substituents adopting equatorial positions (presumably to minimise steric hindrance), literature reports suggest that, with an electron withdrawing substituent on nitrogen, pseudo-allylic strain can dominate to favour a 2,6-*syn*-diaxial arrangement.[10]

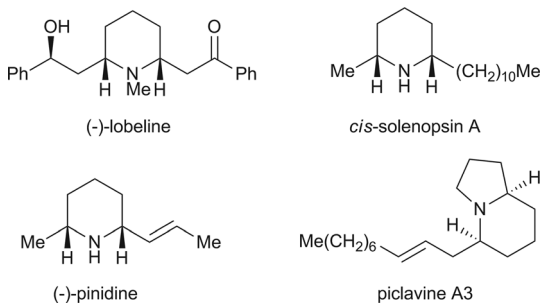
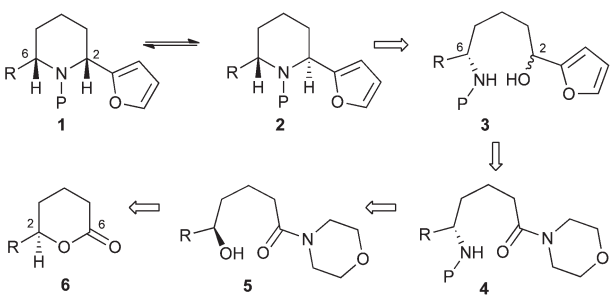


Fig. 1 Some naturally occurring 2,6-*syn*-piperidines.

The general strategy is outlined in Scheme 1. The mixture of *syn* and *anti* piperidines **1** and **2** (which should equilibrate at the 2 position under acidic conditions to the thermodynamically most stable stereoisomer) would result from the acid catalysed dehydrative cyclisation of the 1,5-amino alcohol **3**. This could be formed, as a mixture of C-2 epimers, by reducing the furanyl ketone which would result from displacement of the morpholine in amide **4** with furanyl lithium.[11] If the stereochemically stable amine chiral centre at C-6 was installed using a Mitsunobu reaction of the alcohol **5**, this would lead back to the δ-lactones **6**, several of which, as racemates, are commercially available. The toluene–sulfonyl group was chosen to protect the nitrogen as it would facilitate the Mitsunobu reaction[12] and also be compatible with both the acidic conditions required for the cyclisation/equilibration and the use of furanyl lithium.

The hydroxyl amide (±) **5a** was synthesised from δ-hexalactone as previously reported using morpholine and aluminium chloride (Scheme 2). The hydroxyl group was then displaced by the Boc-Tosyl-amine group using the Mitsunobu protocol with DIAD and PPh_3 to afford the doubly protected amine **7a**. Displacement of the morpholine group by furanyl lithium (generated by reacting the corresponding furan with n-butyllithium in THF) and the subsequent reduction with sodium borohydride could be

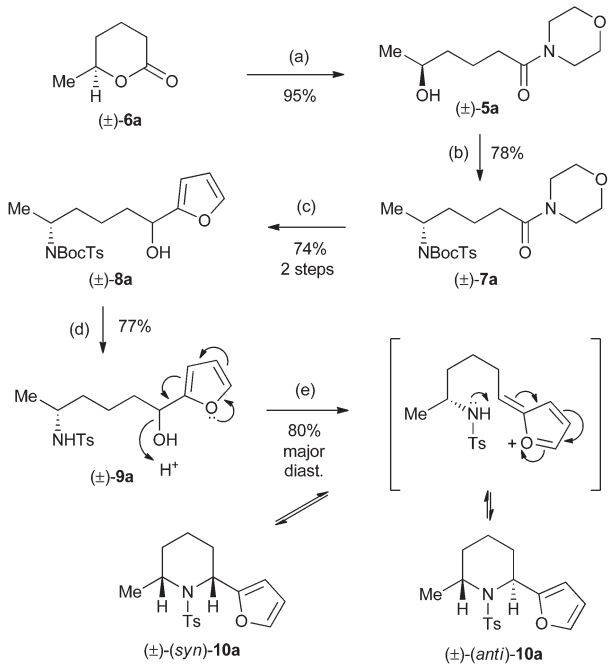


Scheme 1 Retrosynthesis of 2,6-disubstituted piperidines.

[a]*University Chemical Laboratory, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, UK. E-mail: mo263@cam.ac.uk*
[b]*School of Chemistry, Trinity College Dublin, College Green, Dublin, D2, Republic of Ireland*

† Dedicated to Professor E. James Thomas on the occasion of his 65th birthday.

‡ Electronic supplementary information (ESI) available: Experimental procedures and $^{1}H/^{13}C$ NMR data for the sequence (±)-**6a**→ (±)−**10a**. CCDC reference number 85663. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob07008a



Scheme 2 Reagents and conditions: (a) morpholine, $AlCl_3$, DCM; (b) $iPrO_2CN = NCO_2iPr$, PPh_3, BocNHTs, THF; (c) i. furan, *n*-BuLi, THF, ii. $NaBH_4$, MeOH; (d) K_2CO_3, MeOH, Δ; (e) $TsOH{\cdot}H_2O$, $CDCl_3$.

carried out without isolating the intermediate ketone to afford the secondary alcohol **8a** as an approximately 1 : 1 mixture of diastereomers. Initial attempts at an acidic 'one-pot' Boc deprotection and cyclisation resulted in decomposition. Instead, the Boc group was first cleanly removed using potassium carbonate in refluxing methanol to afford the tosyl-amino-alcohol **9a** (Scheme 2). Upon treatment with toluenesulfonic acid in deuterated chloroform, the tosyl-amino-alcohol underwent rapid dehydrative cyclisation to yield the piperidines **10a**. The reaction was most conveniently monitored by ^{1}H NMR spectroscopy. Loss of starting material was essentially complete after around 2 min at room temperature. The initial ratio of product diastereomers at this time was found to be around 1 : 3. Equilibration was slower than the initial cyclisation, taking around 48 h at room temperature. The final thermodynamic diastereomeric ratio was 15 : 1 (the thermodynamically favoured product was the least favoured kinetically). The major product was isolated by direct column chromatography on silica gel, avoiding aqueous workup.

Whilst NMR spectroscopy had assisted in determining that **10a** was formed with high levels of diastereoselectivity, it did not readily reveal what the stereochemistry actually was. However, as the major isomer which formed was crystalline, it was possible to obtain a crystal structure by X-ray diffraction which provided the relative stereochemistry (shown in Fig. 2). As can be seen, the piperidine is 2,6-*syn*-diaxially substituted. Presumably due to the lone pair delocalising into the electron withdrawing tosyl group, the nitrogen is more or less planar. The other substituents seemingly prefer a 2,6-*syn* configuration which allows them to adopt a diaxial conformation, thereby minimising steric clashing with the bulky tosyl group (pseudo-allylic strain).

Given the electron rich nature of the furan group, a mechanism involving formation of a furanyl cation at C-2, as shown in

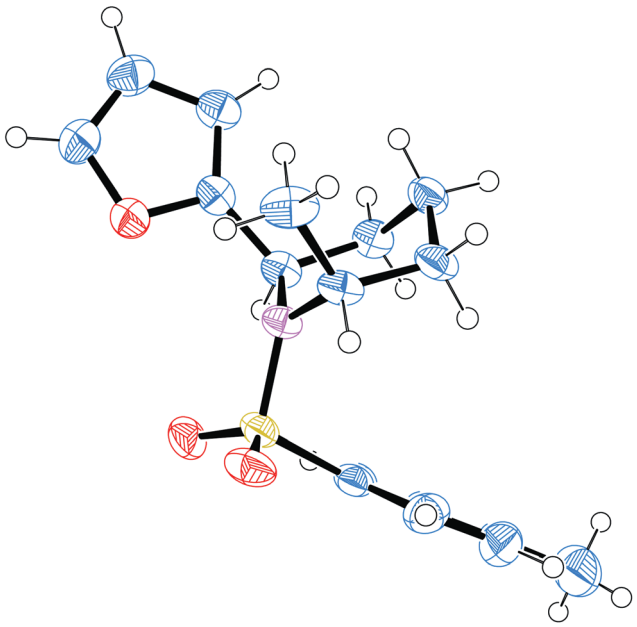
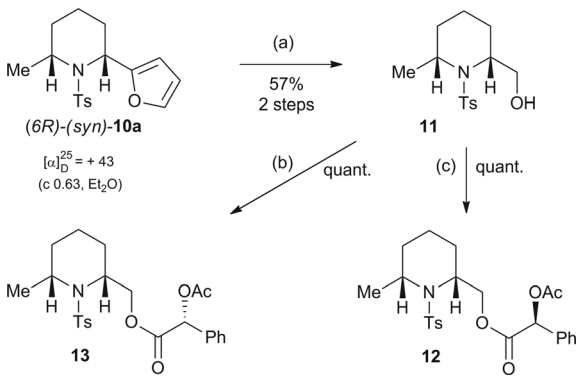


Fig. 2 X-ray structure of (±)-(*syn*)-**10a**. Thermal ellipsoids are shown at the 50% probability level.

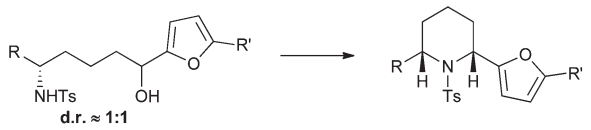
Scheme 2, is plausible. However, epimerisation of either of the C-2 or C-6 chiral centres would lead to the same diastereomer of product. In order to establish that only the furanyl chiral centre was epimerising, the synthetic sequence was repeated with an *enantio*-enriched starting material.

The racemic alcohol (±)-**5a** was selectively acylated in high ee with vinyl acetate using *Candida Antarctica* lipase B, to afford (*S*)-**5a**. This was then taken through the same sequence of reactions shown in Scheme 2, resulting in a furanyl piperidine (6*R*)-*syn*-**10a** which had a measurable optical rotation. The furan group was oxidatively cleaved to the carboxylic acid with catalytic ruthenium trichloride and sodium periodate, followed by borane mediated reduction to the alcohol **11** (Scheme 3). This was then coupled to (*R*)- and (*S*)-acetoxymandelic acids to afford the esters **12** and **13**. Pleasingly, these were both obtained as single diastereomers (whose ^{1}H NMR spectra had several non-overlapping peaks) thus establishing the homochirality of the



Scheme 3 Reagents and conditions: (a) i. $RuCl_3$ (cat.), $NaIO_4$, H_2O, DCM, MeCN, ii. $BH_3{\cdot}SMe_2$, THF (b) (*R*)-acetoxymandelic acid, EDCI, DMAP, DCM; (c) (*S*)-acetoxymandelic acid, EDCI, DMAP, DCM.

Table 1 Results of diastereoselective piperidine formation



Entry	SM	R	R′	Prod.	Yield[a] (%)	dr[b]
1	(±)-**9a**	Me	H	(±)-*syn*-**10a**	80	15 : 1
2	(±)-**9b**	n-C_6H_{11}	H	(±)-*syn*-**10b**	89	25 : 1
3	(±)-**9c**	n-C_9H_{17}	H	(±)-*syn*-**10c**	91	40 : 1
4	(*S*)-**9d**	CH_2OH	H	(6*S*)-*syn*-**10d**	91	18 : 1
5	(*R*)-**9e**	$(CH_2)_3OH$	H	(6*R*)-*syn*-**10e**	88	20 : 1[c]
6	(*R*)-**9a′**	Me	Me	(*R*)-*syn*-**10a′**	93	13 : 1
7	(±)-**9b′**	n-C_6H_{11}	Me	(±)-*syn*-**10b′**	87	25 : 1
8	(±)-**9c′**	n-C_9H_{17}	Me	(±)-*syn*-**10c′**	89	20 : 1
9	(*S*)-**9d′**	CH_2OH	Me	(6*S*)-*syn*-**10d′**	93	29 : 1
10	(*R*)-**9e′**	$(CH_2)_3OH$	Me	(6*R*)-*syn*-**10e′**	85	28 : 1[c]

[a] Isolated yield after chromatography on silica gel. [b] As determined from ^{1}H NMR spectra of reaction mixture. [c] The starting material (which was derived from L-pyroglutamic acid) and product have the opposite configuration to that shown.

piperidine (6*R*)-*syn*-**10a** (and indirectly establishing that both the enzymatic resolution and Mitsunobu reaction proceeded with complete stereoselectivity). As the tosyl-amino-alcohol (*R*)-**8a** was stereodefined at C-6 and a mixture at C-2, it must be the C-2 centre that underwent epimerisation. Stereochemical scrambling at both centres would result in a racemic product.

Having established both the relative and absolute stereochemistry of the piperidine product (6*R*)-*syn*-**10a**, a range of 1,5-tosylamino-alcohols were cyclised under the same conditions. The results are shown in Table 1. The starting materials were diastereomeric mixtures (approximately 1 : 1 in all cases). The yields were generally high and the diastereoselectivities excellent. Hexyl and nonyl derivatives **9b**, **9b′**, **9c** and **9c′** were synthesised from the corresponding δ-lactones according to Scheme 2 and used as racemates. The hydroxymethyl and hydroxypropyl precursors **9d**, **9d′**, **9e** and **9e′** were synthesised from D-serine and L-pyroglutamic acid respectively. In these cases the stereo-random furanyl alcohol chiral centre resulted from addition of lithiated furan (or methyl-furan) to the corresponding aldehyde.

Conclusions

In summary, a highly diastereoselective synthesis of 2,6-*syn*-disubstituted piperidines has been developed which proceeds under acidic conditions with thermodynamic control. It makes use of the electron rich nature of the 2-furyl group and its ability to facilitate epimerisation of an adjacent tosylamine chiral centre. An X-ray crystal structure obtained from one of the products reveals a preference for 2,6-*syn*-diaxial substitution whereby the substituents can avoid an apparent steric clash with the bulky tosyl group on nitrogen (pseudo-allylic strain). Work is underway to further investigate the scope of the reaction, including ring size, and the results will be published in due course.

Acknowledgements

We thank the following for funding: Kinerton/Ipsen, EPSRC (MO'B). We thank Professor Steven V. Ley for supporting this work. We thank the EPSRC for financial assistance towards the purchase of the Nonius-Kappa X-ray diffractometer. We thank Dr John E. Davies for performing the X-ray crystallography work.

Notes and references

1 F. X. Felpin and J. Lebreton, *Tetrahedron*, 2004, **60**, 10127–10153.
2 M. F. Raub, J. H. Cardellina and T. F. Spande, *Tetrahedron Lett.*, 1992, **33**, 2257–2260.
3 S. Leclercq, J. C. Braekman, D. Daloze, J. M. Pasteels and R. K. Van der Meer, *Naturwissenschaften*, 1996, **83**, 222–225.
4 W. H. Tallent and E. C. Horning, *J. Am. Chem. Soc.*, 1956, **78**, 4467–4469.
5 S. J. Danishefsky, S. DeNinno and P. Lartey, *J. Am. Chem. Soc.*, 1987, **109**, 2082–2089; I. Maeba, K. Iwata, F. Usami and H. Furukawa, *J. Org. Chem.*, 1983, **48**, 2998–3002.
6 S. Cahill and M. O'Brien, *Tetrahedron Lett.*, 2006, **47**, 3665–3668.
7 S. Cahill, L. A. Evans and M. O'Brien, *Tetrahedron Lett.*, 2007, **48**, 5683–5686.
8 M. O'Brien, S. Cahill and L. A. Evans, *Chem. Commun.*, 2008, 5559–5561.
9 (*a*) P. R. Girling, T. Kiyoi and A. Whiting, *Org. Biomol. Chem.*, 2011, **9**, 3105–3121; (*b*) J. P. A. Harrity and O. Provoost, *Org. Biomol. Chem.*, 2005, **3**, 1349–1358; (*c*) M. G. P. Buffat, *Tetrahedron*, 2004, **60**, 1701–1729; (*d*) P. M. Weintraub, J. S. Sabol, J. M. Kane and D. R. Borcherding, *Tetrahedron*, 2003, **59**, 2953–2989; (*e*) F.-X. Felpin and J. Lebreton, *Eur. J. Org. Chem.*, 2003 (19), 3693–3712; (*f*) S. Laschat and T. Dickner, *Synthesis*, 2000 (13), 1781–1813; (*g*) V. Baliah, R. Jeyaraman and L. Chandrasekaran, *Chem. Rev.*, 1983, **83**, 379–423.
10 (*a*) Y. L. Chow, C. J. Colon and J. N. S. Tam, *Can. J. Chem.*, 1968, **46**, 2821; (*b*) R. R. Fraser and T. B. Grindley, *Tetrahedron Lett.*, 1974, **15** (47), 4169–4172; (*c*) J. Quick, C. Mondello, M. Humora and T. Brennan, *J. Org. Chem.*, 1978, **43**, 2705–2708; (*d*) P. Beak and W. K. Lee, *J. Org. Chem.*, 1993, **58**, 1109–1117.
11 R. Martin, P. Romea, C. Tey, F. Urpi and J. Vilarrasa, *Synlett*, 1997, **12** (12), 1414–1416.
12 J. R. Henry, L. R. Marcin, M. C. McIntosh, P. M. Scola, G. Davis Harris Jr and S. M. Weinreb, *Tetrahedron Lett.*, 1989, **30**, 5709–5712.

