ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 4836–4838

www.rsc.org/chemcomm

COMMUNICATION

Stereocontrolled access to optically-enriched oxabispidines†

Heloise Brice,[a] Duncan M. Gill,‡*[a] Laura Goldie,[b] Philip S. Keegan,[a] William J. Kerr*[b] and Per H. Svensson[cd]

Received 2nd February 2012, Accepted 22nd March 2012
DOI: 10.1039/c2cc30761h

A range of chiral, optically-enriched bicyclic oxabispidines were prepared from (*S*)-(-)-2,3-epoxypropylphthalimide using an efficient sequence featuring a stereocontrolled intramolecular Mannich reaction as the key transformation.

Over recent years, molecules possessing both the bispidine (**1**; X = CH_2; Fig. 1) and oxabispidine (**1**; X = O) unit have been shown to display a range of biological properties that have made them attractive targets for the pharmaceutical industry. For instance bispidines have been employed in αa4β2 nicotinic acetylcholine receptor ligands as potential neuroprotective agents,[1] and the oxabispidine ring system (**1**; X = O) has been strategically embedded within molecules showing a range of potential medicinal applications, including use as atrial repolarisation-delaying agents in the treatment of cardiac arrhythmia (AstraZeneca),[2] mTOR and PI3 kinase inhibitors (Wyeth),[3] $P2X_7$ receptor antagonists/interleukin-1β inhibitors (AstraZeneca),[4] and Factor Xa inhibitors (GlaxoSmithKline).[5] The lupine alkaloid, (−)-sparteine **2**,[6] also has the bispidine structure (**1**; X = CH_2) at its core, with this natural product having been employed as the key chiral ligand in an extensive array of enantioselective transformations.[7]

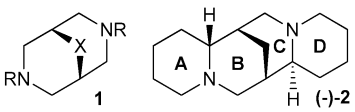
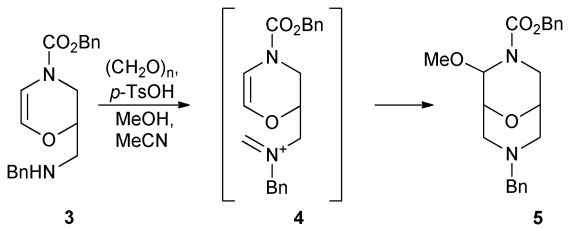


Fig. 1 Bridged bicyclic diamines **1** and **2**.

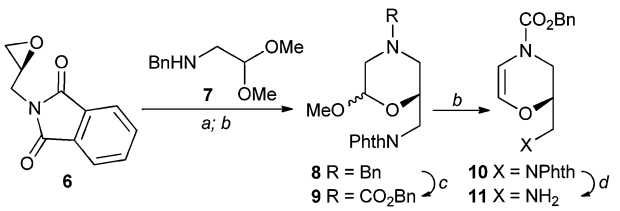
Indeed, the rigid and central 3,7-diazabicyclo[3.3.1]nonane backbone within (−)-sparteine **2** is believed to be crucial to the chiral induction within such asymmetric processes (*vide infra*).[8] In contrast, chiral oxabispidines (**1**; X = O) have been the focus of significantly less attention as ligands for use in enantioselective organic reactions, despite the potentially similar chiral environment predicting that these species could act as effective surrogates for the bispidine-based, sparteine **2**. Although some stereoselective routes to oxabispidines have emerged recently, the available methods tend to be limited by (i) the requirement for more than one pre-formed chiral substrate, (ii) relatively lengthy synthetic pathways, and (iii) a lack of flexibility relating to the substituent groups that can be introduced around the oxabispidine core.[9]



Scheme 1 Intramolecular Mannich cyclisation.

As part of a search for efficient methods of preparing oxabispidines,[10] we disclosed[11] the intramolecular Mannich cyclisation of oxazine **3** shown in Scheme 1.[12,13]

Based on this established precedent, we envisaged that preparation of chiral amine **11** and engagement with a range of higher aldehydes would potentially open expedient access to a series of optically-enriched and further functionalised oxabispidines. According to this strategy and as depicted in Scheme 2, commercially available (*S*)-(−)-2,3-epoxypropyl-phthalimide **6** provided the key chiral starting material. This species underwent ring opening with amine **7**; following a solvent swap to toluene and addition of catalytic acid, heating at reflux

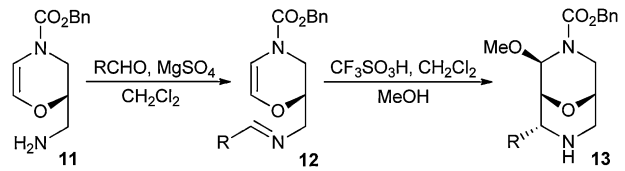


Scheme 2 Preparation of amine precursor **11**. **Reaction Conditions** *a*: Ethanol, reflux; *b*: TsOH (10 mol%), toluene, reflux; *c*: $ClCO_2Bn$, CH_2Cl_2, r.t.; *d*: $MeNH_2$, EtOH, reflux.

[a] *Pharmaceutical Development, AstraZeneca R&D Charnwood, Bakewell Road, Loughborough LE11 5RH, UK*
[b] *Department of Pure and Applied Chemistry, University of Strathclyde, 295 Cathedral Street, Glasgow, G1 1XL, UK. E-mail: w.kerr@strath.ac.uk; Fax: +44 (0)141 548 4822; Tel: +44 (0)141 548 2959*
[c] *Pharmaceutical Development, AstraZeneca R&D Sodertalje, S-151 85 Södertälje, Sweden*
[d] *Applied Physical Chemistry, Department of Chemistry, Royal Institute of Technology (KTH), SE-100 44 Stockholm, Sweden*
† Electronic supplementary information (ESI) available: experimental procedures and characterisation data for compounds **8–14** and **16–21**. See DOI: 10.1039/c2cc30761h
‡ Current Address: Department of Chemical and Biological Sciences, University of Huddersfield, Queensgate, Huddersfield, HD1 3DH, UK. E-mail: d.m.gill@hud.ac.uk; Fax: +44 (0)1484 472182; Tel: +44 (0)1484 473337.

resulted in cyclisation to form acetal **8**.[14] Prolonged exposure to these conditions did not result in any further elimination of methanol to give the oxazine. Consequently, conversion of the benzylamine to the corresponding CBz protected amines **9** was secured in a single step by treatment with benzylchloroformate.[15] Exposure of **9** to refluxing toluene/catalytic acid resulted in smooth elimination to deliver oxazine **10** in 67% yield over 4 steps after silica gel chromatography. Whilst deprotection of the phthalimide with hydrazine[16] liberated **11** in an acceptable 70% yield, use of a more practically convenient procedure[17] with the less toxic methylamine delivered this key chiral unit **11** in a more appreciable 87% yield without recourse to chromatography.

With amine **11** now readily accessible on scale, appropriate conditions to allow a chemo- and stereoselective annulation process were investigated.§ Initially, the key chiral substrate **11** was coupled with a range of aldehydes to give imines **12**, generally as a single geometric (*E*) isomer. Following the screening of a range of Lewis and Brønsted acids, under a series of conditions, treatment of **12** with 1 molar equivalent of trifluoromethanesulfonic acid (TfOH) at −20 °C resulted in immediate consumption of the imine substrate. Although isolation and characterisation of intermediate species so formed was not possible, analysis by ^{1}H NMR spectroscopy indicated that neither the imine, nor the oxazine olefinic protons were present at this stage. Accordingly, addition of 1 molar equivalent of methanol resulted in formation of the oxabispidine hemiaminal ether **13** (Scheme 3; Table 1), as a single diastereomer in generally good to excellent yields.



Scheme 3 Formation of imines **12** and Mannich cyclisation to give oxabispidine acetals **13**.

The ^{1}H NMR spectrum of **13a** (which is typical of the series) gives the appearance of a mixture of two isomers; variable temperature studies showed that this is, in fact, due to restricted rotation between stable conformations of the carbamate,

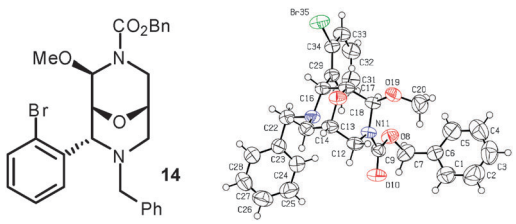
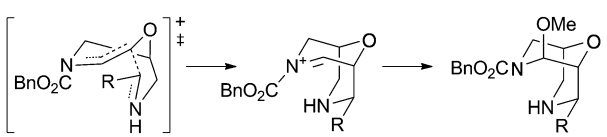


Fig. 2 The molecular structure of **14** with the thermal displacement ellipsoids set at 50% probability and hydrogen atoms as spheres of arbitrary radius.



Scheme 4 Postulated mechanistic pathway.

Table 1 Scope of cyclisation and summary of oxabispidines prepared

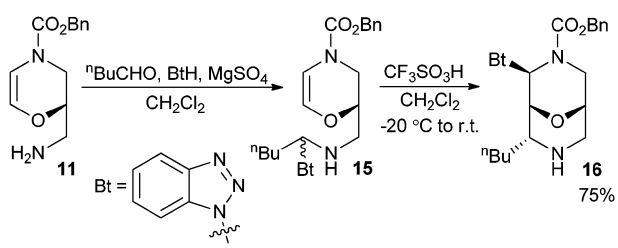
Entry	*R*	Method[a]	Acetal	Yield
1	Ph	A	**13a**	92
2	*o*-BrC_6H_4	A	**13b**	96
3	*p*-$MeOC_6H_4$	B	**13c**	93
4	*o*-$CF_3C_6H_4$	A	**13d**	76
5	^{t}Bu	A	**13e**	90
6	*c*-Hex	A	**13f**	76
7	^{n}Bu	A	—	0
8	^{n}Bu	C	**16**	75

[a] Method **A**: CF_3SO_3H, MeOH, CH_2Cl_2, −20 °C to r.t.; **B**: *p*-TSA (10 mol%), MeOH, 65 °C; **C**: CF_3SO_3H, BtH, CH_2Cl_2, −20 °C to r.t.

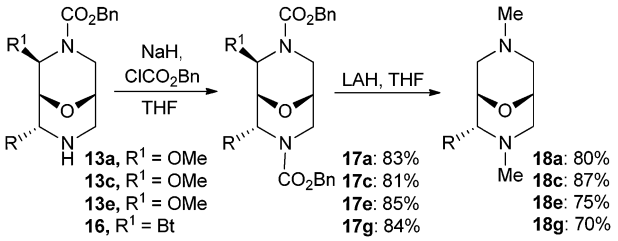
a feature also observable in the spectra of oxazines **10–12**. Careful assignment of spectra and nOe experiments revealed that the R-substituent is disposed equatorially, and that the –OMe group occupies an axial position. Confirmation of these assignments was provided by a single crystal X-ray diffractogram of benzyl protected compound **14** (Fig. 2).[18] Accordingly, these outcomes are consistent with a chair-like transition state, as shown in Scheme 4, in which the imine geometry is conserved, followed by attack of methanol on the least hindered face of the iminium ion.

As shown in Table 1, this cyclisation process was applied successfully to a range of aldehydes. Notably, the imine derived from electron-rich *p*-methoxybenzaldehyde did not react under the standard TfOH conditions, with more forcing conditions being required to deliver oxabispidine **13c** (entry 3). Additionally, although steric bulk does not appear to compromise reactivity (entries 5 & 6), aldehydes bearing more than one α-hydrogen did not work well (entry 7). This is attributable to the propensity of amine **11** to catalyse competing aldol-type polymerisation of the aldehyde. This drawback was overcome by utilising Katritzky's technique of stabilising reactive aldehydes as the benzotriazole adduct.[19] As shown in Scheme 5, addition of one equivalent of benzotriazole, followed by the aldehyde, led to formation of an intermediate with a complex ^{1}H NMR spectrum assigned as **15**. Pleasingly, cyclisation to the oxabispidine acetal **16** occurred smoothly upon treatment with TfOH, although full conversion required that the reaction be run for 18 h at r.t. Additionally, within this revised protocol we discovered that the liberated benzotriazole was a competent nucleophile, leading to direct formation of the stable adduct **16**.

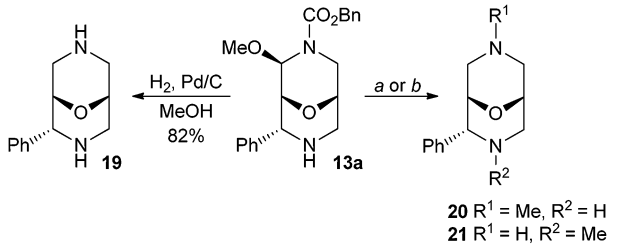
With a view to accessing compounds of this class which would have application in asymmetric synthesis, the further functional manipulation of the product oxabispidines was targeted. In this regard and as shown in Scheme 6, compounds **13a**, **c**, and **e**, and **16** were treated with benzyl chloroformate, followed by LAH to give the corresponding *N*,*N*′-dimethyl



Scheme 5 Preparation of oxabispidines from an aliphatic aldehyde.



Scheme 6 Conversion of oxabispidine acetals to diamines **18**.



Scheme 7 Elaboration of **13a** to deliver an array of amine substitution. **Reaction Conditions** *a*: LAH, Et_2O, **20**, 72%; *b*: (i) MeI, K_2CO_3, CH_2Cl_2, 73%; (ii) H_2, Pd/C, MeOH, **21**, 92%.

oxabispidines **18a**, **c**, **e**, and **g** (R = Ph; *p*-$MeOC_6H_4$; ^{t}Bu; and ^{n}Bu, respectively) in good yields over two steps.

Compound **13a** was chosen as a vehicle to demonstrate the inherent flexibility of this class of intermediate and, as shown in Scheme 7, was efficiently converted to *bis*-2^y amine **19**, and both complementary monomethyl compounds **20** and **21**.

Having now established an efficient route to optically-enriched oxabispidine structures, the relationship of these species with sparteine-type molecular architectures is worthy of note. As recently shown by O'Brien, sparteine surrogates (without the D ring unit) are superior to the full sparteine structure within certain asymmetric applications.[20] However, access to (−)-sparteine surrogates is not presently available. In relation to this, structures **13/16** map directly onto the B/C rings within (−)-sparteine **2**, whilst providing functionality to allow further structural manipulations. Furthermore, employment of the commercially available enantiomeric (*R*)-glycidyl phthalimide, (*R*)-**6**, will deliver the opposite chiral oxabispidine series, equivalent to the known (+)-sparteine surrogates.[7] These features add further to the preparative flexibility and utility of the routes developed here.

In summary, a range of *C*-substituted oxabispidines have been prepared from a commercially available chiral building block, using a novel stereoselective intramolecular Mannich reaction. The route is highly modular and amenable to creation of a wide range of analogues where diversity is incorporated late in the synthetic sequence. Further studies directed towards the stereoselective synthesis of other classes of bridged heterobicyclic compounds with potential pharmaceutical and catalytic applications are ongoing within our laboratories.

We thank Ms T. Weber and Mr K. Munro (Univ. of Strathclyde) and Drs A. R. Burns and J. Pavey (AZ) for additional contributions, and the EPSRC Mass Spectrometry Service, Univ. of Wales, Swansea, and H. Pancholi (AZ) for analyses.

Notes and references

§ During initial investigations, amine **11** readily performed double alkylation processes when exposed to conditions similar to those shown in Scheme 1.

1 A. Mazurov, L. Miao, Y.-D. Xiao, P. S. Hammond, C. H. Miller, S. R. Akireddy, V. S. Murthy, R. C. Whitaker, S. R. Breining and M. S. Melvin, *PCT Int. Appl.*, 2008, Application: WO 2008-057938.
2 A. Bjoere, D. Cladingboel, G. Ensor, A. Herring, J. Kajanus, R. Lundqvist, C. Olsson, C.-G. Sigfridsson and G. Strandlund, *PCT Int. Appl.*, 2006, Application: WO 2006-SE688 20060612.
3 A. Zask, J. A. Kaplan, J. C. Verheijen, K. J. Curran, D. J. Richard and S. Ayral-Kaloustian, *U.S. Pat. Appl. Publ.*, 2009, Application: US 2008-251712 20081015.
4 M. Furber, L. Alcaraz, J. E. Bent, A. Beyerbach, K. Bowers, M. Braddock, M. V. Caffrey, D. Cladingboel, J. Collington, D. K. Donald, M. Fagura, F. Ince, E. C. Kinchin, C. Laurent, M. Lawson, T. J. Luker, M. M. P. Mortimore, A. D. Pimm, R. J. Riley, N. Roberts, M. Robertson, J. Theaker, P. V. Thorne, R. Weaver, P. Webborn and P. Willis, *J. Med. Chem.*, 2007, **50**, 5882.
5 C. Chan, J. N. Hamblin, H. A. Kelly, N. P. King, A. M. Mason, V. K. Patel, S. Senger, G. P. Shah, N. S. Watson, H. E. Weston, C. Whitworth and R. J. Young, *PCT Int. Appl.*, 2002, Application: WO 2002-GB2586 20020606.
6 D. Hoppe and T. Hense, *Angew. Chem. Int. Ed.*, 1997, **36**, 2282; O. Chuzel and O. Riant, *Top. Organomet. Chem.*, 2005, **15**, 59.
7 For examples of the use of (−)-sparteine and (+)-sparteine as chiral ligands, see: P. O'Brien, *Chem. Commun.*, 2008, 655.
8 M. J. Dearden, C. R. Firkin, J.-P. R. Hermet and P. O'Brien, *J. Am. Chem. Soc.*, 2002, **124**, 11870; A. J. Dixon, M. J. McGrath and P. O'Brien, *Org. Synth.*, 2006, **83**, 141.
9 M. Breuning and M. Steiner, *Synthesis*, 2007, 1702; M. Breuning and M. Steiner, *Tetrahedron: Asymmetry*, 2008, **19**, 1978; M. Breuning, M. Steiner, C. Mehler, A. Paasche and D. Hein, *J. Org. Chem.*, 2008, **74**, 1407.
10 L. Cheema, D. Cladingboel and R. Sinclair, *PCT Int. Appl.*, 2002, Application: WO 2002-08360; L. Cheema and D. Cladingboel, *PCT Int. Appl.*, 2002, Application: WO 2002-083691; D. Cladingboel, *PCT Int. Appl.*, 2004, Application: WO 2004-035592.
11 D. M. Gill, *PCT Int. Appl.*, 2003, Application: WO 2003-045956; D. M. Gill, H. Holness and P. S. Keegan, *Abstracts of Papers, 232nd ACS National Meeting*, San Francisco, 2006.
12 For other examples of such cyclisation reactions, see C. Chan, S. Zheng, B. Zhou, J. Guo, R. M. Heid, B. J. D. Wright and S. Danishefsky, *Angew. Chem., Int. Ed.*, 2006, **45**, 1749; K. C. Nicolaou, B. S. Safina, M. Zak, S. H. Lee, M. Nevalainen, M. Bella, A. A. Estrada, C. Funke, F. J. Zécri and S. Bulat, *J. Am. Chem. Soc.*, 2005, **127**, 11159.
13 For intermolecular reactions of oxazines with electrophiles, see: L. Eberson, M. Malmberg and K. Nyberg, *Acta Chem. Scand., Ser. B*, 1984, **38b**, 345.
14 H. Ito, Y. Ikeuchi, T. Taguchi, Y. Hanzawa and M. Shiro, *J. Am. Chem. Soc.*, 1994, **116**, 5469.
15 A. Commerçon and G. Ponsinet, *Tetrahedron Lett.*, 1985, **26**, 4093.
16 T. Sasaki, K. Minamoto and H. Itoh, *J. Org. Chem.*, 1978, **43**, 2320.
17 S. E. Sen and S. L. Roach, *Synthesis*, 1995, 756.
18 Crystallographic data for the compound reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 835119. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; email: deposit@ccdc.cam.ac.uk). Further crystallographic information is available within the ESI.
19 A. R. Katritzky, *Tetrahedron*, 1991, **47**, 2683.
20 G. Carbone, P. O'Brien, K. R. Campos, I. Coldham and A. Sanderson, *J. Am. Chem. Soc.*, 2010, **132**, 7260; D. Stead, G. Carbone, P. O'Brien and G. Hilmersson, *J. Am. Chem. Soc.*, 2010, **132**, 15445.

