Stereocontrolled access to optically-enriched oxabispidines†

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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 = CH₂; 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 α4β2 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 P2X7 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 = CH₂) at its core, with this natural product having been employed as the key chiral ligand in an extensive array of enantioselective transformations.7

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

As part of a search for efficient methods of preparing oxabispidines,10 we disclosed11 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-epoxypropylphthalimide 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 1 Intramolecular Mannich cyclisation.

Scheme 2 Preparation of amine precursor 11. Reaction Conditions a: Ethanol, reflux; b: TsOH (10 mol%), toluene, reflux; c: ClCO₂Bn, CH₂Cl₂, r.t.; d: MeNH₂, EtOH, reflux.

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resulted in cyclisation to form acetal 8.\textsuperscript{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 benzyl chloroformate.\textsuperscript{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\textsuperscript{16} liberated 11 in an acceptable 70\% yield, use of a more practically convenient procedure\textsuperscript{7} with the less toxic methyamine 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.\textsuperscript{6} 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.

\begin{equation}
\text{CO}_{2}\text{Bn} \quad \text{CHO} \quad \text{MgSO}_4 \quad \text{CH}_2\text{Cl}_2 \quad \text{MeOH} \quad \text{CH}_2\text{Cl}_2
\end{equation}

Scheme 3 Formulation 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, with an arbitrary radius. Ellipsoids set at 50\% probability and hydrogen atoms as spheres of arbitrary radius.

**Table 1** Scope of cyclisation and summary of oxabispidines prepared

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Method\textsuperscript{a}</th>
<th>Acetal</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>A</td>
<td>13a</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>(\alpha)-BrC(_2)H(_4)</td>
<td>A</td>
<td>13b</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>(p)-MeOC(_2)H(_5)</td>
<td>B</td>
<td>13c</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>(\alpha)-CF(_3)C(_6)H(_4)</td>
<td>A</td>
<td>13d</td>
<td>76</td>
</tr>
<tr>
<td>5</td>
<td>(\beta)-Bu</td>
<td>A</td>
<td>13e</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>(\gamma)-Hex</td>
<td>A</td>
<td>13f</td>
<td>76</td>
</tr>
<tr>
<td>7</td>
<td>(\beta)-Bu</td>
<td>C</td>
<td>16</td>
<td>75</td>
</tr>
</tbody>
</table>

\(\text{a}\) Method A: CF\(_3\)SO\(_3\)H, MeOH, CH\(_2\)Cl\(_2\), -20 °C to r.t.; B: \(p\)-TSA (10 mol\%), MeOH, 65 °C; C: CF\(_3\)SO\(_3\)H, BtH, CH\(_2\)Cl\(_2\), -20 °C to r.t.

Careful assignment of spectra and nOe experiments revealed that the R-substituent is disposed equatorially, and that the \(-\text{OMe}\) 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).\textsuperscript{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 \(\alpha\)-hydrogen did not work well (entry 7). This is attributable to the propensity of amine 11 to catalyst competing aldol-type polymerisation of the aldehyde. This drawback was overcome by utilising Katritzky’s technique of stabilising reactive aldehydes as the benzotriazole adduct.\textsuperscript{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...
Conversion of oxabispidine acetals to diamines

Scheme 6

Conversion of oxabispidine acetals to diamines

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>H</td>
<td>18a, 80%</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>18b, 75%</td>
</tr>
<tr>
<td>Me</td>
<td>Et</td>
<td>18c, 87%</td>
</tr>
<tr>
<td>Me</td>
<td>OMe</td>
<td>17a, 83%</td>
</tr>
<tr>
<td>Me</td>
<td>OMe</td>
<td>17c, 81%</td>
</tr>
<tr>
<td>Me</td>
<td>OMe</td>
<td>17e, 75%</td>
</tr>
<tr>
<td>Et</td>
<td>OMe</td>
<td>17g, 84%</td>
</tr>
</tbody>
</table>

oxabispidines 18a, c, e, and g (R = Ph; p-MeOC6H4; 1Bu; and 2Bu, 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-19 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 series, equivalent to the known (+)-sparteine surrogates.7 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.

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Notes and references

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


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) 1223-336-433; email: deposit@ccdc.cam.ac.uk). Further crystallographic information is available within the ESL.
