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Flexible access to conformationally-locked bicyclic morpholines†

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A preparatively accessible route to a series of conformationally-locked bicyclic morpholines has been developed. This flexible approach allows for diversification in order for a small array of lead-like scaffolds to be synthesised from readily available key building blocks.

Through an appreciable range of recent endeavours, bridged heterocycles have emerged as desirable synthetic targets within the pharmaceutical industry. More specifically, molecules containing the bispidine (1; X = CH2; Fig. 1) and oxabispide (1; X = O) unit have become increasingly popular due to their evolving range of therapeutic attributes.1 In relation to this, we have recently disclosed a convenient, modular, and amenable route for the synthesis of a range of chiral, optically-enriched bicyclic oxabispide structures.2 Our preparative approach embedded specific key building blocks into the desired molecular scaffold and, in turn, exploited an intramolecular Mannich reaction (IMR) at the heart of our overall synthetic strategy. In this regard, using emerging preparative routes that have allowed the systematic exploration of chemical space, MacLellan and Nelson have very recently established a conceptual framework for analysing, planning, and extending synthetic approaches to diverse lead-like scaffolds,3 and, indeed, highlighted the applicability of our methods for access to the aforementioned series of flexibly functionalised oxabispides.2 Following on from this, based on their potential therapeutic properties and driven by the lack of flexible methods for their preparation,4 our extended studies in this area have focused on strategies towards a series of differentially-functionnalised, strained, and synthetically more challenging bridged bicyclic morpholines, such as 2. Moreover, our approaches here aimed to further underpin the recently developing concepts around the enhancement of preparative effectiveness aligned with lead-like diversity.3

Our general preparative approach towards the synthesis of such bridged morpholine units is illustrated in Fig. 2. Key oxazine 5, bearing a pendant electrophilic unit within the structure, will be selectively cyclised to compounds of structure type 6; intermediates of type 5 will be synthesised from commercially available glycidol 3 and readily prepared amine acetal 4 as the key starting units. Overall, the synthetic approach described herein allows for diversification at the 2, 6, and 7 positions of the overall bridged morpholine scaffold.

According to this proposed strategy, our initial target molecule was aldehyde 10. As noted above, the synthesis begins with commercially available glycidol 3, which was protected prior to undergoing ring opening with amine acetal 4 (Scheme 1). The addition of sub-stoichiometric quantities of protic acid5 resulted in efficient formation of core morpholine acetal 8. Alcohol deprotection and subsequent oxidation, under Swern conditions, delivered the desired aldehyde 10 in high overall yield.

With aldehyde 10 now accessible on good scale, the installation of the additional functionality required for access to the...
[3.2.1] bridged bicyclic structure 15 was investigated (Scheme 2). Following appreciable Wittig optimisation, Barbier conditions were employed to provide morpholine derivative 11 in an acceptable 59% yield. Subsequently, an amine protecting group switch was carried out in order to facilitate the elimination of methanol and install the desired double bond in 12.2a Hydroboration–oxidation then gave 13, which, after further oxidation, delivered cyclisation precursor 14. Following the screening of a variety of Bronsted acids, it was found that p-toluenesulfonic acid in the presence of methanol facilitated the key 5-exo-trig cyclisation process to deliver the targeted bridged bicyclic morpholine scaffold in a pleasing 71% yield.

Analysis of NMR data revealed that our key cyclisation process was completely diastereoselective, with compound 15 being obtained as a single diastereomer. In order to authenticate the relative stereochemistry, NOESY experiments were performed; interpretation of the nOe interactions established that the bridging oxygen, the methoxy unit, and the alcohol functionality were situated on the same face of the bridged bicyclic structure, as shown in Fig. 3.

With the overall aim of targeting a variety of bridged morpholine units, the developed synthetic approach allows for points of structural diversification to be introduced late in the synthetic pathway, leading to maximised preparative efficiencies. For example, 15 was converted into the corresponding ketone 16 (Scheme 3). Subsequent nucleophilic addition with methylmagnesium chloride produced derivative 17 in a good 72% yield and as a single diastereomer.

With the cyclisation approach to the novel bridged bicyclic morpholine structures established, our studies continued towards the preparation of more heavily substituted analogues. Envisaging that our developed cyclisation protocol would be amenable to further substitution on the ethylene bridge, the previously synthesised aldehyde 10 was reacted with methylmagnesium chloride to produce alcohol 18 in excellent yield (Scheme 4). Following oxidation, the previously described amine protecting group switch and elimination were carried out to deliver compound 20. Wittig olefination, followed by a hydroboration–oxidation sequence produced alcohol 22, which, on further oxidation, delivered cyclisation precursor 23, all in good yields. We were then pleased to realise that our previously developed cyclisation protocol also facilitated the formation of the alternative bridged morpholine unit, although this time as a mixture of diastereomers (24/25, 7:3 dr).

Evidence from NOESY NMR experiments revealed that within the major diastereomer (24) the bridging oxygen, the methoxy unit, the methyl group, and the alcohol moiety were all positioned on
with structure 16, ketone 26 was reacted with methyllithium chloride to deliver alcohol derivative 27 as a single diastereomer.

In summary, we have established a preparatively flexible strategy for access to a series of novel bridged morpholine units. Moreover, it is believed that both the use of readily available starting materials and the ability to perform late-stage structural manipulations further enhance the effectiveness of the approach described. Indeed, it is important to highlight that the directing stereocentre within this overall sequence is provided by the glycidol building block (3) at the very outset of our synthetic pathway. Accordingly, this overall approach has the potential to enhance the available synthetic strategies towards diverse lead-like scaffolds for application in a range of therapeutic areas. Further studies towards the establishment of associated asymmetric routes are currently on-going within our laboratories.

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Notes and references


