Rapid Asymmetric Synthesis of Arene and Heteroarene Fused Azacycles: Enantiopure Building Blocks for Medicinal Chemistry

This proposal seeks to develop efficient methods for the asymmetric synthesis of a range of enantiopure, highly functionalised arene and heteroarene fused azacycles (Fig. 1). Compounds containing these molecular architectures have great potential as enantiopure building blocks owing to the extensive range of biological activities which they exhibit.[1,2]

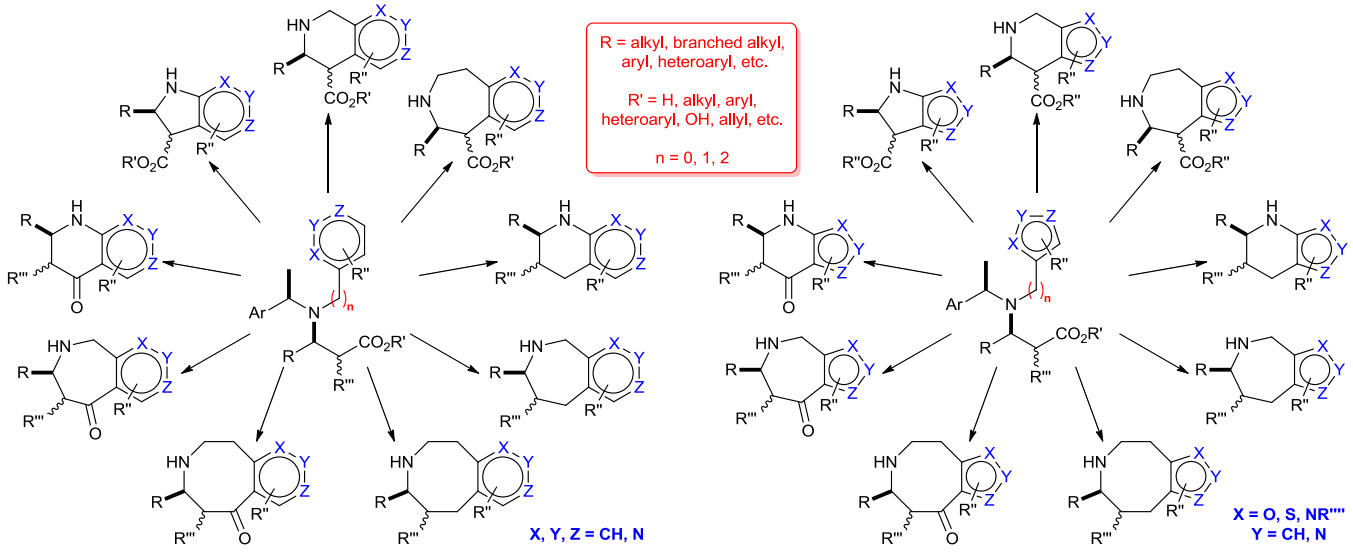
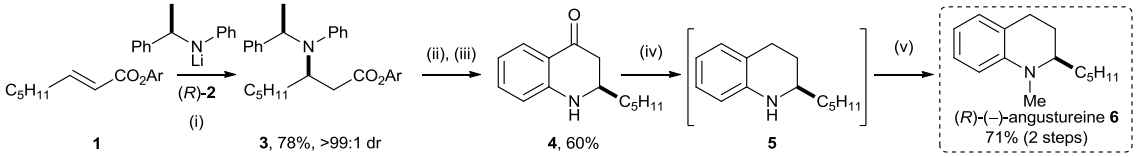


Figure 1. Proposed library of enantiopure arene and heteroarene fused azacycles.

The proposed programme of work will involve development of methods to effect the cyclisation of a range of enantiopure β-amino esters (or their derivatives) bearing aryl, arylmethyl or 2-arylethyl groups on the nitrogen atom (or the corresponding heteroaryl analogues) via: (i) Friedel-Crafts type acylation; (ii) Friedel-Crafts type alkylation of the corresponding β-amino alcohols; or (iii) Friedel-Crafts type alkylation by activation of an α-hydroxyl group. A structurally diverse range of these β-amino and α-hydroxy-β-amino esters can be accessed using our well established lithium amide conjugate addition methodology.[3]

Pilot studies

Recent studies conducted within the Davies group have demonstrated the short and concise asymmetric synthesis of the tetrahydroquinoline alkaloid (*R*)-(–)-angustureine **6** employing an acid-mediated Friedel-Crafts type cyclisation to construct the azacyclic motif. In the key stereodefining step in this synthesis, the conjugate addition of lithium (*R*)-*N*-phenyl-*N*-(α-methylbenzyl)aminde **2** to *p*-methoxyphenyl ester **1** proceeded with excellent diastereoselectivity to give **3** in 78% yield and >99:1 dr. Saponification of **3** and subsequent cyclisation via treatment with polyphosphoric acid (PPA) proceeded with in situ loss of the α-methylbenzyl group to give **4** in 60% yield. Further functional group manipulation afforded enantiopure (*R*)-(–)-angustureine **6** in 71% yield over 2 steps (Scheme 1).[4]



Scheme 1. *Reagents and conditions:* (i) (*R*)-**2**, THF, –78 °C, 2 h; (ii) LiOH, THF/H_2O, 40 °C, 3 h; (iii) PPA, 100 °C, 16 h; (iv) $LiAlH_4$, THF, reflux, 16 h; (v) MeI, K_2CO_3, THF, reflux, 16 h. [Ar = *p*-methoxyphenyl].

Proposed programme of work

(i) Initial studies: conjugate addition of lithium amides bearing heteroaryl substituents

Building upon our well-established and scalable conjugate addition methodology,[3] the student will initially prepare a range of β-amino esters **9** and **11** (R''' = H) from α,β-unsaturated esters **7** using the conjugate addition of a range of enantiopure lithium amides **8** and **10** (which can be readily derived from either antipode of commercially available α-methylbenzylamines), to include the novel *N*-heteroaryl (**8** or **10**, n = 0), *N*-(heteroarylmethyl) (**8** or **10**, n = 1) and *N*-[(2-hetereoaryl)ethyl] (**8** or **10**, n = 2) substituted derivatives. This strategy will enable the incorporation of a wide range of heterocycles into the key β-amino ester templates **9** and **11**, to include substituted furans, thiophenes and pyrroles, as well as pyridines and diazines. The syntheses of the corresponding benzo-fused templates will also be investigated upon conjugate addition of lithium amides **13–16**. Further development of this strategy will include in situ functionalisation of the intermediate enolate formed upon conjugate addition, via either oxidation with camphorsulfonyloxaziridine (CSO) **12** or alkylation, to access a range of α-substituted-β-amino esters (Fig. 2). Once these initial studies have been completed, the main focus of this investigation will be the development of efficient cyclisation strategies using a Friedel-Crafts type approach, based upon intramolecular acylation or alkylation.

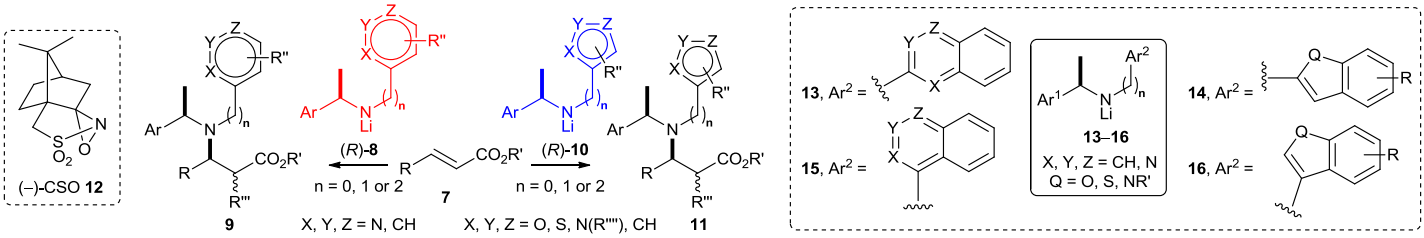


Figure 2. Conjugate addition of novel lithium amides bearing heteroaryl substituents.

(ii) Cyclisation strategy I: via a Friedel-Crafts type acylation protocol

A reliable method to effect the intramolecular Fridel-Crafts type acylation of β-amino esters **9** or **11** upon attack of the aryl moiety at the carbonyl group of an activated derivative **17** or **19** will initially be developed for a range of simple carbocyclic β-amino esters (i.e., **9** when X, Y, Z = CH). The subsequent incorporation of heterotoms within this system would then give access to a wide range of the corresponding substituted bicycles **18** and **20** including substituted tetrahydrothienopyridines, tetrahydrofuronopyridines and tetrahydropyrrolopyridines, as well as tetrahydrothienoazepines, tetrahydrofuroazepines and hexahydropyrroloazepines. In cases where cyclisation onto the phenyl ring of the α-methylbenzyl group is competitive with cyclisation onto the heteroaryl moiety, simple protecting group manipulation may be employed to obviate this reaction pathway (e.g., the introduction of an electron withdrawing substituent on the α-methylbenzyl fragment). With a working knowledge of the inherent substitution preferences of the various hetereoaryl moieties in hand, substituent effects may be probed within this reaction manifold to increase further the structural diversity of accessible azacycles **18** and **20** (Fig. 3).

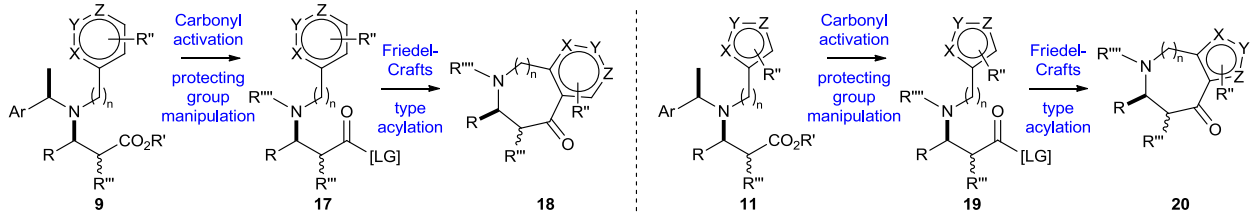


Figure 3. Asymmetric syntheses of azacylic scaffolds via Friedel-Crafts type acylation. [LG] = leaving group; n = 0, 1, 2.

(iii) Cyclisation strategy II: via a Friedel-Crafts type alkylation protocol

An alternative cyclisation strategy will employ intramolecular Friedel-Crafts type alkylation rather than acylation, through initial reduction of the ester moieties within **9** and **11** (with *N*-protecting group manipulation, as necessary), followed by activation of the resultant alcohols to cyclisation (**21** and **23**) onto the pendant aryl/heteroaryl moiety, to give bicycles **22** and **24**. As in the case of acylation, the regioselectivity of the cyclisation will be probed in the case of simple carbocyclic β-amino esters (i.e., **9** when X, Y, Z = CH) and heteroaryl analogues will subsequently be screened. These compounds may also be accessed through reduction of bicycles **18** and **20**, prepared via the acylation route described above, and the relative efficacy of the two alternative strategies will be evaluated (Fig. 4).

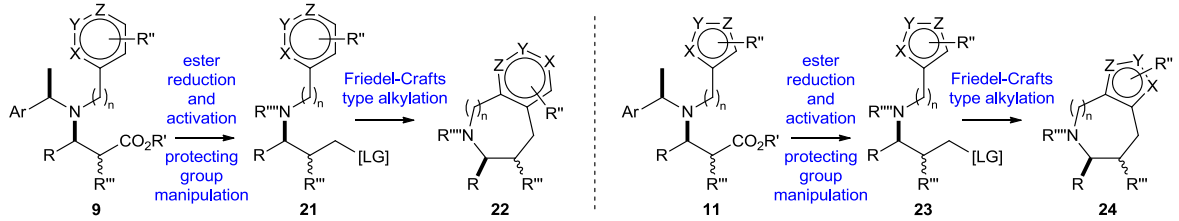


Figure 4. Asymmetric syntheses of azacylic scaffolds via Friedel-Crafts type alkylation. [LG] = leaving group; n = 0, 1, 2.

(iv) Cyclisation strategy III: via activation of an α-hydroxyl group

A range of enantiopure α-hydroxy-β-amino esters **25** and **28** will be prepared using our highly diastereoselective aminohydroxylation protocol.[3,5] The resultant 2,3-*anti*-α-hydroxy-β-amino esters may then be epimerised by an oxidation/diastereoselective reduction protocol to provide access to the corresponding 2,3-*syn*-diastereoisomers of the cyclisation precursors. Activation of the α-hydroxyl groups within **25** and **28** upon treatment with either MsCl, TsCl, or Tf_2O, for example, is then anticipated to promote intramolecular Friedel-Crafts type alkylation to give a wide range of arene fused azacycles, all bearing an ester substituent which provides a handle for further functionalisation of these scaffolds. Once a reliable procedure has been established for the simple carbocyclic substrates (i.e., **25** when X, Y, Z = CH), the analogous compounds containing heteroaryl groups will also be evaluated in this reaction manifold (Fig. 5).

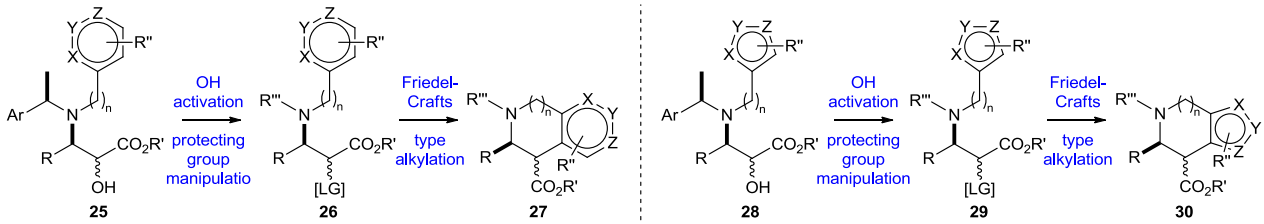


Figure 5. Asymmetric syntheses of azacylic scaffolds via activation of an α-hydroxyl group. [LG] = leaving group; n = 0, 1, 2.

Conclusions

In conclusion, the development of this methodology would enable the rapid synthesis of a library of enantiopure arene and heteroarene fused azacycles. These classes of compounds are known to display potent biological activities, and therefore the synthesis and biological evaluation of a range of analogues (e.g., different regio- and stereoisomers/different ring sizes/different substitution patterns/introduction of heteroatoms, etc.) has huge potential.

References

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