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Internal nucleophilic catalyst mediated cyclisation/ring expansion cascades for the synthesis of medium-sized lactones and lactams

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Abstract: A strategy for the synthesis of medium-sized lactones and lactams from linear precursors is described in which an amine acts as an internal nucleophilic catalyst to facilitate a novel cyclisation/ring expansion cascade sequence. This method obviates the need to use high-dilution conditions usually associated with medium-ring cyclisation protocols, as the reactions operate exclusively via kinetically favourable 'normal' sized cyclic transition states. This same feature also enables biaryl-containing medium-sized rings to be prepared with complete atroposelectivity via point-to-axial chirality transfer.

Introduction

Medium-sized rings have much promise in medicinal chemistry^{1,2} but are difficult to prepare via conventional cyclisation methods.³ Destabilising transannular interactions and loss of entropy during cyclisation mean that medium ring cyclisation reactions of the type $1 \rightarrow 2$ (Scheme 1a) typically suffer from competing intermolecular reactions or other side processes.^{4,5} Synthetic routes to access medium-sized rings that avoid end-to-end cyclisation are therefore desirable, and ring expansion reactions have proven to be especially useful in this context.^{6,7}

In this manuscript, a new process is described by which medium-sized rings can be accessed directly from simple linear precursors. The avoidance of medium-sized cyclic transitions states is key to our design principle, in which we use a nucleophilic catalyst built into the linear starting material to promote a cyclisation/ring expansion cascade. For example, while the direct synthesis of 10-membered ring 2 from a hypothetical linear precursor 1 (Scheme 1a) is usually a slow/difficult process,⁴ we reasoned that similar medium-sized ring frameworks would be more effectively synthesised from alternative linear precursors of the form 3, in which a reactive motif 'Z' built into the linear starting material mediates a cyclisation/ring expansion cascade $(3 \rightarrow 4$ \rightarrow 5, Scheme 1b).^{8,9} By designing the reactions so that both discrete cyclisation reactions proceed via 'normal'-sized cyclic transition states (especially if they are 5- or 6-membered), it is reasonable to expect that a kinetically more favourable reaction course will be followed, as illustrated in the stylised reaction coordinate for these two scenarios depicted in Scheme 1c. By allowing this lower energy pathway to operate, medium-sized ring transition states can be avoided, which should help to reduce side

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reactions and obviate the need to use impractical high dilution/pseudo high dilution conditions that are common in typical medium-sized ring and macrocycle cyclisation reactions.¹⁰

The realisation of this strategy is reported herein. Thus, a method based on the formation ($6 \rightarrow 7$) and spontaneous expansion ($7 \rightarrow 8$) of reactive acyl-ammonium ion intermediates is described that enables nitrogen-containing medium-sized rings to be prepared from simple linear precursors (Scheme 1d). Using these cascade reactions, we show that a wide range of functionalised medium-sized lactones and lactams (40 examples, 31–100% yield) can be prepared under mild, practical reaction conditions. Furthermore, in suitably designed cases, biaryl containing medium-sized rings can also be formed with complete atroposelectively via a new type of point-to-axial chirality transfer reaction.¹¹



Scheme 1. a) Direct medium ring cyclisation; b) cyclisation/ring expansion; c) hypothetical reaction coordinates; d) This work - Internal nucleophilic catalyst mediated cyclisation/ring expansion cascade reactions.

Results and Discussion

We started by examining pyridine-containing linear precursor **9a** [see Supporting Information (SI) for its synthesis]. The plan was that activation of carboxylic acid **9a** would initiate a cyclisation (**9a** \rightarrow **10a**) and ring expansion (**10a** \rightarrow **11a**) cascade. Thus, carboxylic acid **9a** was treated with T3P (propanephosphonic acid

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anhydride) and NEt(*i*-Pr)₂ in chloroform¹² and, after stirring for just 30 min at RT, the desired 10-membered lactone **11a** was formed and isolated in 90% yield. Of further interest, **11a** was formed exclusively as the single atropisomer shown, with the structural and stereochemical assignment supported by X-ray crystallographic data¹³ (Scheme 2; the atroposelectivity aspects of this reaction, including data that confirms that atropoisomerisation by free rotation is not an energetically feasible process for this system, are discussed later in the manuscript).



Scheme 2. Cyclisation/ring expansion cascade synthesis of 11a.

Given the known challenges of forming 10-membered ring lactones,^{3a,4} the efficiency of this reaction was highly encouraging, especially as it was performed under mild conditions at standard dilution. Nonetheless, to discount the possibility that this is simply an unusually efficient 10-membered ring lactonisation, hydroxy acid 12a (analogous to 9a but lacking the pyridine nitrogen) was reacted under the same conditions used to make **11a** (with a 5 h reaction time. Scheme 3a). As expected, none of the analogous 10-membered lactone was formed, with dimeric 20-membered lactone 12b the only tractable product isolated from this reaction, corroborating the importance of the pyridine nitrogen in mediating the synthesis of 11a. Furthermore, our novel cyclisation/ring expansion cascade also works well using an aliphatic tertiary amine as the internal nucleophilic catalyst in place of the pyridine; thus, linear hydroxy acid 13a was converted into 9-membered lactone 14a in 76% yield (T3P, 30 min, RT), whilst an intractable mixture of products resulted when the analogous nitrogen-free hydroxy acid 15a was reacted under the same conditions (Scheme 3b).



Scheme 3. a) Formation of 20-membered head-to-tail dimer 12b; b) cyclisation/ring expansion cascade synthesis of 14a and failed synthesis of 15b.

The scope of the reaction is broad and is summarised in Scheme 4. 10-Membered lactone **11b** was formed without problem using the standard method, whilst the homologous 11-membered lactone **11c** was also prepared, albeit in lower yield, which is likely to be a result of this example proceeding via a less favourable 7-membered transition state. Conversely, the synthesis of the smaller 9-membered product **11d** failed, presumably due to there being too much strain in the sp² rich scaffold. Next, a range of secondary alcohol-based systems were then tested, and the reactions worked well in all cases; functionality at various positions of the starting material, protected amine handles, diazine and DMAP-like tethers and tertiary alcohols all being well-tolerated, with lactones **11e–p** isolated in consistently high yields.

The same strategy can also be used to make medium-sized lactams using unprotected amine-based nucleophiles. Using the standard protocol, lactam **11q** was formed in 50% yield; competing intermolecular amide bond-formation likely accounts for the decreased yield, which is supported by the observation that a significantly higher yield was obtained when the same reaction was performed at increased dilution (78%). Other secondary amine-based systems performed similarly under the standard undiluted conditions (**11r**–**v**). Pleasingly, aniline-based lactam **11u** was formed in quantitative yield; presumably, this system did not suffer from competing intermolecular reaction in view of the lower nucleophilicity of the aniline nucleophile relative to aliphatic amines. Finally, we found that primary amine-derived lactam **11v** could be formed in 52% yield using the standard conditions.¹⁴

Medium-sized lactones **14a–m** were also prepared from aliphatic tertiary amine-containing hydroxy acids **13a–m**. The yields were generally good across this series, with broad scope demonstrated; it is especially noteworthy that the cascade reactions can be used to prepare lactones right across the 'medium-sized' ring range, with 8–11-membered lactones all being prepared using the standard protocol. The utility of the cyclisation/ring expansion cascade has therefore been well demonstrated by the synthesis of 34 medium-sized lactones or lactams using a simple and mild synthetic method, without requiring high dilution conditions.

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Scheme 4. Cyclisation/ring expansion cascade reactions of pyridine and tertiary amine containing hydroxy acids and amino acids.

An important feature of these reactions is the observation that in all examples containing two stereochemical units, the products were exclusively formed as single diastereoisomers (11a, 11e-o and 11q-v; all contain a point stereogenic center and an unsymmetrical biaryl unit with axial chirality). Thus, the point chirality of the secondary nucleophile is able to fully control the formed atropisomer in the medium-sized cyclic biaryl product in all of these cases, via what is to the best of our knowledge, an unprecedented type of point-to-axial chirality transfer.11 Atropisomerism can play a vital role in mediating ligand-target interactions in biology,15 but while synthetic methods able to impart exquisite levels of control over stereogenic centres on a single atom (usually referred to as point chirality) are very well established, methods designed to control other chirality elements (e.g. planar, axial and helical chirality)¹⁶ are less well developed.¹⁷ Atroposelective methods capable of delivering medium-sized rings or macrocycles are particularly rare,¹⁸ which encouraged us to examine the atroposelectivity of our cascade reactions in more detail.

First, we confirmed that the biaryl unit in the medium-sized ring products is unable to undergo free rotation. Based on its geometry and ring size, we predicted that the sp²-rich medium-ring scaffold **11a** would be relatively rigid and that rotation about the biaryl C–C single bond is unlikely to be kinetically accessible; indeed, to the best of our knowledge, compound **11a** is the smallest ring system based on an unbridged 1,2-disubsituted and 1,3-disubstituted biaryl framework in the literature. Related larger

macrocyclic scaffolds containing similar biaryl motifs have also been shown to exist as stable atropisomers at room temperature,^{19,20} nonetheless, for additional support, we modelled the energy required to rotate about this bond using DFT (Scheme 5). Starting from the crystal structure of **11a**, this was optimised at the BP86/SV(P) level and scans were performed whilst rotating the biaryl dihedral angle in both directions, reoptimising the structure at each step. No minima were found from these calculations and the energies calculated increased steeply to give values that can be considered chemically inaccessible, strongly suggesting that the biaryl unit is indeed unable to rotate freely (see SI for tabulated data).

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Scheme 5. Calculated BP86/SV(P) electronic energies for 11a with a SCRF solvent correction in CHCl₃. Energies given are for geometry optimised structures at fixed biaryl dihedral angles.

One hypothesis for the excellent stereoselectivity, which is depicted in Scheme 6 for prototypical substrate **11a**, is a kinetic argument that hinges on the stereochemistry-determining step operating via a 6-membered transition state. The observed stereochemical outcome is consistent with the alcohol attacking the prochiral intermediate *N*-acyl ammonium ion with the methyl group in a pseudo-equatorial orientation in a chair/boat-like conformation (*c.f.* $\mathbf{A} \rightarrow \mathbf{B}$, Scheme 6a). Conversely, to generate the unobserved isomer **11a**', attack on the opposite face of the *N*-acyl ammonium ion is required, which necessitates that the methyl group be oriented in a pseudo-axial conformation, the transition state for which ($\mathbf{C} \rightarrow \mathbf{D}$) is likely to be higher in energy.²¹



Scheme 6. Proposed atroposelectivity model: a) A kinetic model based on diastereoselective attack into prochiral *N*-acyliminium ion $(\mathbf{A} \rightarrow \mathbf{B})$; b) a thermodynamic model based on reversible ring expansion/ring contraction.

An alternative explanation is that the reactions are reversible and under thermodynamic control (Scheme 6b). This model is

supported by DFT calculations of the ground state energies of **11a** and **11a'**; thus, the Gibbs free energy of the observed and unobserved atropisomers **11a** and **11a'** were calculated at the M06-2X/6-311G* level of theory (see SI for full details)²² and the observed isomer **11a** was calculated to be 22 kJ/mol lower in free energy than the unobserved isomer **11a'**. Such a large energy difference would provide a clear driving force for the selective formation of **11a** if the reactions are reversable.

The atroposelectivity was also probed experimentally (Scheme 7). Thus, substrates with the methyl substituent transposed α - to both the phenyl and pyridyl rings were prepared and tested in the cyclisation/ring expansion cascade (11w and 11x). Both reactions worked very well in terms of conversion and yield, but the atroposelectivity was low compared with 11a. This suggests that the position a- to the nucleophile is special in terms of its ability to control the biaryl stereochemistry. Therefore, we next examined the steric influence of this position using unsvmmetrical tertiary alcohol nucleophiles (11v-zb). Interestingly, a clear trend of increasing atroposelectivity was observed as the alcohol substituents become more different in size; low atroposelectivity was observed for 11y (methyl vs. allyl), modest atroposelectivity for 11z (methyl vs. phenyl) and complete atroposelectivity was restored for 11za and 11zb (methyl vs. tertbutyl).



Scheme 7. Cyclisation/ring expansion cascade reactions of pyridine containing point stereogenic centers and the calculated free energy difference between the two atropoisomeric forms.

This atroposelectivity trend is consistent with the kinetic argument outlined in Scheme 6a (with the large substituent presumably adopting the pseudo-equatorial conformation). However, the thermodynamic model cannot be ruled out either, especially as DFT calculations of the relative free energy of the two possible atroposelectivity; a large difference in free energy was calculated for the atroposelective examples (**11a**, **11za**, **11zb**, $\Delta G = 22-26$ kJ/mol) whereas the least selective examples can be considered

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isoenergetic at this level of theory (**11x**, **11y**, $\Delta G = 2$ kJ/mol). This arguably favours the thermodynamic model, but caution should be exercised when interpreting these results, as the calculated difference in free energies of the products may simply serve as an approximation for the difference in free energy of the analogous transition states that lead to their formation (especially given that the products and transitions states might be expected to have reasonably similar geometries). Indeed, it may be that either/both models operate in different examples. Ascertaining which operates in any given reaction system is therefore difficult, however, what is clear is that for high atroposelectivity to be achieved synthetically, the key is having either a secondary nucleophile, or an unsymmetrical tertiary nucleophile with a significant size difference between its substituents.

Finally, since the point-to-axial chirality transfer is a diastereoselective process, it is straightforward to prepare enantioenriched biaryl-products simply by using an enantioenriched nucleophile. Thus, as a simple proof-of-concept, enantioenriched (\approx 71% *ee*) lactam **11v** was formed in 51% overall yield from **16** (72% *de*) following acidic cleavage of the Ellman's auxiliary, ester hydrolysis and cyclisation/expansion in the usual way (Scheme 8).²³



Scheme 8. Synthesis of enantioenriched planar chiral lactam 11v.

Conclusion

In summary, a cyclisation/ring expansion cascade reaction protocol has been developed for the synthesis of 10-membered cyclic biaryl systems from simple pyridyl-based linear carboxylic acids. The novel strategy simultaneously addresses two important synthetic challenges: 1) achieving efficient and reliable end-to-end cyclisations of medium-sized rings from linear precursors; 2) effectively controlling atroposelectivity in the resulting cyclic products in biayrl-based systems. The cyclisation/ring expansion cascade strategy is also applicable to simple tertiary amine containing hydroxy acids to make 8-11membered lactones, which greatly extends its scope and potential utility. Thus, the synthetic methods reported should facilitate the practical and selective synthesis of biologically important medium-sized rings, whilst a new strategy for generating planar chiral medium rigs via point-to-axial chirality transfer is also introduced.

Experimental Section

Full experimental details can characterisation data are included in the SI. An exemplar synthetic procedure for the cyclisation/ring expansion cascade is provided for the synthesis of 10-membered lactone **11a**.

4-Methyl-4,5-dihydro-6,10-(azeno)benzo[d][1]oxacyclododecin-

2(1H)-one (11a) To a stirring solution of 2-(2-(6-(2-hydroxypropyl)pyridin-2-yl)phenyl)acetic acid 9a (44.0 mg, 0.163 mmol) in chloroform (3 mL), was added diisopropylethylamine (50.0 µL, 0.302 mmol), followed by the addition of T3P (78.0 mg, 0.284 mmol, 156 mg of a 50% solution in ethyl acetate). Upon the addition of T3P, the solution rapidly changed from a colourless to an orange solution. After stirring for 30 mins at r.t., the solution was concentrated and purified via flash column chromatography (SiO₂, 1:1 ethyl acetate:hexane) to afford the title compound 11a as a pale yellow solid (37 mg, 90%); Rf 0.45 (3:7 ethyl acetate:hexane); m.p. 110-114 °C; v_{max}/cm⁻¹ (thin film) 3063, 2973, 2928, 1720, 1586, 1575, 1450, 1422; δ_H (400 MHz, CDCl₃) 7.80–7.78 (1H, m, ArH), 7.69 (1H, t, J = 7.6 Hz, ArH), 7.54 (1H, d, J = 7.6 Hz, ArH), 7.43–7.40 (3H, m, ArH), 7.04 (1H, dd, J = 7.6, 0.5 Hz, ArH), 5.64–5.55 (1H, m, OCH), 3.65 (1H, d, J = 14.5 Hz, CHHCO), 3.54 (1H, d, J = 14.5 Hz, CHHCO), 3.12-3.00 (2H, m, NCCH₂), 1.50 (3H, d, J = 6.4 Hz, CH₃); δ_C (100 MHz, CDCI₃) 174.3 (CO), 155.6 (ArC), 154.9 (ArC), 137.2 (ArC), 137.0 (ArC), 135.1 (ArC), 133.9 (ArC), 129.2 (ArC), 127.9 (ArC), 127.7 (ArC), 121.0 (ArC), 118.4 (ArC), 70.4 (OCH), 44.4 (CO-CH₂), 40.4 (NCCH₂), 21.4 (CH₃); HRMS (ESI): calcd. for $C_{16}H_{16}NO_2$ 254.1176. Found: [MH]⁺, 254.1173 (1.0 ppm error).

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Keywords: medium-sized rings • ring expansion • atropisomers• pyridines • axial chirality

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- [22] To compare the energies of the possible diastereoisomers, the structures were optimised at the M06-2X/6-311G* level, followed by frequency calculations at the same level. These structures were confirmed as minima by the absence of imaginary frequencies. The M06-2X/6-311G* SCF energies were corrected for their zero-point energies, thermal energies and entropies obtained from the frequency calculations. Optimisations were performed with tight convergence criteria and no symmetry constraints were applied. An ultrafine integral grid was used for all calculations. Solvent corrections were applied with the Polarisable Continuum Model (PCM) using the integral equation formalism variant (IEFPCMO). Energies in Hartrees and xyz coordinates are reported in the SI.
- [23] Enantiomer ratios were determined using chiral HPLC (see SI). Partial overlap of signals means that there may be a small amount of error in the absolute ee value assigned, but what is clear that qualitatively, the chirality transfer was successful. Further studies will be needed to build on these preliminary data in the future.

RESEARCH ARTICLE

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RESEARCH ARTICLE



A strategy for the synthesis of medium-sized lactones and lactams from linear precursors is described in which an amine acts as an internal nucleophilic catalyst to facilitate a cyclisation/ring expansion cascade sequence. This method obviates the need to use high-dilution-type conditions and enables medium-sized ring biaryl scaffolds to be prepared with full control of atroposelectivity via point-to-axial chirality transfer.

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Internal nucleophilic catalyst mediated cyclisation/ring expansion cascades for the synthesis of medium-sized lactones and lactams