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Iterative Assembly of Macrocyclic Lactones using Successive Ring Expansion Reactions

Thomas C. Stephens, Aggie Lawer, Thomas French, and William P. Unsworth

Abstract: Macrocyclic lactones can be prepared from lactams and hydroxyacid derivatives via an efficient 3- or 4-atom iterative ring expansion protocol. The products can also be expanded using amino acid-based linear fragments, meaning that macrocycles with precise sequences of hydroxy- and amino acids can be assembled in high yields by “growing” them from smaller rings, using a simple procedure in which high dilution is not required. The method should significantly expedite the practical synthesis of diverse nitrogen containing macrolide frameworks.

Introduction

Nature routinely makes use of exquisitely selective assembly line-type processes\(^{(1)}\) to construct molecules vital to life, such as DNA and polyketide metabolites,\(^{(2)}\) and artificial synthetic methods based on similar principles have long been known for the synthesis of peptides\(^{(3)}\) and oligonucleotides,\(^{(4)}\) thus transforming synthetic biology and its associated fields. Indeed, the value of assembly line type approaches is increasingly being recognised for the preparation of other compound classes: seminal methods include those for the synthesis of sugars,\(^{(5)}\) polyketide derivatives,\(^{(6)}\) sp\(^3\)-rich hydrocarbons,\(^{(7)}\) polyenes,\(^{(8)}\) cyclic ethers,\(^{(9)}\) polyaromatics\(^{(10)}\) and various others.\(^{(11)}\)

This manuscript concerns our efforts to develop a practical, iterative method for the assembly of macrocyclic lactones. Medicinal interest in macrocycles has risen markedly in recent years,\(^{(12, 13)}\) with macrocyclic lactones (especially macrolide antibiotics)\(^{(14)}\) featuring heavily in medicinally oriented research. Naturally occurring macrolides such as erythromycin \(^{14a}\) have long been used as antibiotics, while analogues prepared via semi-synthesis (e.g. azithromycin \(^{2f,g}\)) as well as fully synthetic analogues (e.g. \(^{3}\))\(^{(14b)}\) have since been developed to address the challenge of rising anti-microbial resistance (Figure 1).\(^{(15)}\)

Macrocyclic lactones (and indeed most macrocycles) are usually difficult to make, largely due to the energetic barriers that must be overcome to promote the end-to-end cyclisation of a linear precursor.\(^{(16)}\) Nonetheless, several powerful strategies have emerged over the years to address this,\(^{(17, 18)}\) with ring closure via the lactone C–O bond (e.g. the Yamaguchi macrolactonisation reaction) and ring closing metathesis amongst the most popular.\(^{(18)}\) However, such methods usually rely on high dilution conditions to favour macrocyclisation over competing dimerisation or oligomerisation pathways, and this impacts their practicality.\(^{(16)}\) Furthermore, macrocyclisation reactions are typically highly sensitive to structural and conformational changes in the cyclisation precursors. This means that generalised, building block approaches to prepare macrocyclic lactones are rare, although a notable exception is the excellent work of Seiple, Zhang, Myers and co-workers, in which a modular platform for the efficient synthesis of > 300 macrolide antibiotic candidates (c.f. 3, Figure 1) is described.\(^{(14)}\)

In terms of developing a general, practical route to macrocyclic lactones, ring expansion strategies have much potential,\(^{(19, 20)}\) as the end-to-end cyclisation step that hampers conventional macrocyclisation methods is completely avoided. Thus, in this manuscript, we describe the development of a high yielding, iterative strategy for the synthesis of macrocyclic lactones using Successive Ring Expansion (SuRE) reactions.\(^{(21)}\)

The new synthetic protocols reported enable a broad array of functionalised lactone- and lactam-containing macrocycles (10–24-membered) to be prepared in high yields by the iterative insertion of both hydroxy acid and amino acid-based linear fragments into lactams (Figure 2).

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Results and Discussion

Previous research in our group has focused on the development of ring expansion routes to macrocyclic lactams, although we recently uncovered two examples of lactone-forming reactions that operate via a similar strategy. Thus, following N-acylation of lactam 4a, the resulting imides (6/7a) were shown to undergo hydrogenolysis (to form alcohols 8/9a) and rearrange via cyclols 10/11a to furnish ring expanded lactones 12a and 13a (Scheme 1). Unlike in our previous lactam work, ring expansion did not take place spontaneously following protecting group cleavage (an equilibrating mixture of isomers 8/9a, 10/11a, and 12/13a was formed in each case) but stirring this mixture in chloroform was sufficient to drive the equilibrium towards ring expanded macrocyclic lactones 12a and 13a, which were isolated in 88 and 47% yields, respectively.

To establish whether these proof-of-concept results could be expanded into a general method, we began by evaluating the effect of the ring size of the starting lactam on the reaction outcome. Ring size was predicted to have a major impact on the alcohol/cyclol/lactone equilibrium shown in Scheme 1; in particular, the expansion of normal ring sizes (5–7-membered) into medium-sized rings (8–11-membered) was expected to be challenging, in view of the well-known difficulties associated with making medium-sized rings. To facilitate this, a total of 20 N-acylated derivatives 6a–j and 7a–j were prepared, using 4–13-membered lactams 4a–j and α- and β-hydroxyacidic derivatives 5a and 5b, which were coupled using a high yielding, lactam N-acylation procedure summarised in Scheme 2.

We then moved on to examine their ring expansion reactions, starting with the α-hydroxyacid derivatives 6a–j. Although we had already shown that ring-expanded lactone 12a could be made in high yield from 6a, literature precedent suggested that other ring sizes would not be so easy; for example, imides 6c–6e have been described previously in separate studies by Shemayakin, Antonov and co-workers and Griot and co-workers, but in their hands were found to produce mixtures of alcohol (8) and cyclol (10) products following hydrogenolysis, with no evidence for having undergone ring expansion. However, when our hydrogenolysis conditions were applied to novel imide 6f, N,O-acetal 15f was unexpectedly formed in 87% yield, presumably via reduction of a dehydrated intermediate of the form A (Scheme 3). The same process also operates on other ring sizes, with N,O-acetals 15d–h all being formed similarly, from their respective imides 6d–h (Scheme 3 box).

While this discovery represents an interesting way to prepare cyclic N,O-acetals, it was problematic in the context of generating ring-expanded lactones. A solution was found by changing the hydrogenolysis solvent; thus, if the hydrogenolysis was carried out in methanol, intermediate A was trapped by the solvent to form a methanol adduct (14f) that is stable with respect to over-reduction and was isolated in 95% yield. We then considered that by exchanging methanol for water, a water-trapped adduct (i.e. cyclol 10f) would form similarly, and serve as an intermediate towards the desired ring expansion lactone. Pleasingly this idea worked well; thus, the hydrogenol-
alysis was performed in a mixed THF/water solvent system, and following filtration, the reaction mixture (which at this stage was largely comprised of cyclol 10f) was stirred in chloroform/NEt$_3$ at RT, which promoted clean isomerisation to the desired ring expansion product 12f in 89% yield (Scheme 3).

Having established a viable hydrogenolysis method in which over-reduction can be avoided, this procedure was applied to all of the 4–13-membered cyclic imide precursors 6a–j (Scheme 4). From these experiments, a clear trend emerged linking the size of the cyclic starting material 6 to the reaction outcome. Thus, in the cases of 4- and 5-membered cyclic imides 6a and 6b, debenzylation proceeded smoothly, but isomerisation did not occur following stirring in chloroform/NEt$_3$, with imides 8b and 8c being isolated in high yields. Conversely, under the same conditions, 6- and 7-membered imides 8d and 8e only partially rearranged; cyclol isomers 10d and 10e were formed as the major products in CDCl$_3$ solution, although this compound exists as a 3:2 ratio of 10d:8d. (a) For simplicity, the major isomeric form of 10d is drawn, but in CDCl$_3$ solution, this compounds exists as a 69:13:1 ratio of 10e:8e:12e.

Thus, both the α- and β-hydroxyacid series have a clear point at which the ring expansion reactions “switch on”, that is ≥8-membered rings expand effectively in the α-hydroxyacid series, and ≥6-membered for their β-hydroxyacid analogues. Of course, there will likely be some substrate specific variation, but these size guidelines should be helpful in predicting the viability of ring expansion processes on related systems. We believe that these are thermodynamic outcomes, and that following hydrogenolysis, the three isomeric forms (cyclol or ring expanded isomers, whereas the ring expanded form of undergoing ring expansion or remaining as the imide form) were formed as the major products in CDCl$_3$ solution, although the corresponding imide and ring expanded isomeric forms were also visible in their $^1$H NMR spectra. Finally, all the cyclic imides from 8-membered 6f to 13-membered 6a underwent hydrogenolysis and ring expansion as desired, to deliver ring expanded products 12f–j and 12a in high yields (83–97%).

We then examined β-hydroxyacid derivatives 7a–j. Helpfully, in this series over-reduction was not observed, hence hydrogenolysis could be performed in ethyl acetate, and was followed by stirring in chloroform/NEt$_3$ as before. Again, clear ring size trends emerged; as in the α-hydroxyacid series, the 4- and 5-membered ring starting materials 7b and 7c failed to undergo ring expansion following hydrogenolysis, with alcohols 9b and 9c being isolated instead, but all cyclic imides from 6-membered 7d to 13-membered 7a were successfully converted into the desired ring expansion products 13d–j and 13a in high yields (85–96%, Scheme 5).

Thus, the relative Gibbs free energies of isomeric imide (8/9), cyclol (10/11) and ring expanded products (12/13) were calculated for the four reaction systems which lie on the borderline of undergoing ring expansion or remaining as the imide form (i.e. those leading to the formation of 8c, 12f, 9c and 13d) with these results summarised in Table 1. Pleasingly, the calculations agree with the synthetic outcomes; thus, for the α-hydroxyacid series, the 5-membered ring imide form 8c was calculated to be significantly lower in energy than either the cyclol or ring expanded isomers, whereas the ring expanded form 12f was calculated to have the lowest Gibbs free energy for the 8-membered starting material. A similar trend was also seen for the β-hydroxyacid series, in which the switch in the reaction outcome between the 5- and 6-membered starting materials observed synthetically was predicted by the DFT calculations.27,28

Full details of the computational methods can

![Scheme 4](image)

Scheme 4. Ring expansion of α-hydroxyacid derivatives 6a–j. (a) For simplicity, the major isomeric form of 10d is drawn, but in CDCl$_3$ solution, this compound exists as a 3:2 ratio of 10d:8d. (b) For simplicity, the major isomeric form of 10e is drawn, but in CDCl$_3$ solution, this compound exists as a 69:13:1 ratio of 10e:8e:12e.

![Scheme 5](image)

Scheme 5. Ring expansion of β-hydroxyacid derivatives 7a–j.
produced mixtures of products (8d/10d/12d and 8e/10e/12e). In these cases, the three isomeric forms 8/10/12 were found to be much closer in Gibbs free energy in comparison to those shown in Table 1, with no isomer being >3 kcal mol⁻¹ lower in Gibbs free energy than each of the other two, hence it is not surprising that a mixture of products was obtained in the synthetic reactions; indeed, these results further corroborate the notion that the reactions are under thermodynamic control.

We next went on to examine more complex reaction systems and test whether the products could be further elaborated in successive ring expansion reactions (Scheme 6). Additional starting materials were required for this phase of the work, all of which were either commercially available, or easily prepared via literature routes, with further details included in the Supporting Information (Scheme 6 box). The yields given in Scheme 6 refer to the overall acylation/deprotection/ring expansion reactions. For all Procedures A–C: i) lactam (1 equiv), Pyridine (6 equiv), DMAP (0.1 equiv), ROCl (1.5 equiv), CH₂Cl₂ (0.1 mL), 18 h, 45 °C, then: Procedure A: ii) H₂, Pd/C in H₂O/THF; iii) NEt₃, CHCl₃, 18 h, RT (for XPG = OBn, m = 1) Procedure B: ii) H₂, Pd/C in EtOAc; iii) NEt₃, CHCl₃, 18 h, RT (for XPG = OBn, m = 2) Procedure C: ii) DBU (10 equiv), CH₂Cl₂, 18 h, RT (for XPG = NRFmoc, m = 1 or 2). [a] An additional 1.5 equiv of ROCl 5a was used in the N-acylation (step i) to help ensure complete conversion; [b] An additional 4.5 equiv of ROCl 5a was used in the N-acylation (step i) to help ensure complete conversion.

Table 1. DFT [B3LYP/6-31G*] calculated relative Gibbs free energy values (in vacuum) for isomeric imides (8/9), cyclols (10/11) and lactones (12/13).[^1][^2]

| n  | m  | Ring sizes | 8/9 | 10/11 | 12/13 |
|----|----|------------|-----|-------|-------|
| 2  | 1  | 5 → 8      | 0.0 (8c) | 13.4 (10c) | 10.3 (12c) |
| 5  | 1  | 8 → 11     | 6.3 (8f) | 8.9 (10f) | 0.0 (12f) |
| 2  | 2  | 5 → 9      | 0.0 (9c) | 11.7 (11c) | 4.1 (13c) |
| 3  | 2  | 6 → 10     | 2.4 (9d) | 8.1 (11d) | 0.0 (13d) |

[^1]: Table 1. DFT [B3LYP/6-31G*] calculated relative Gibbs free energy values (in vacuum) for isomeric imides (8/9), cyclols (10/11) and lactones (12/13).
[^2]: Other starting materials used.

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pansion sequence and are all real synthetic yields of purified products following column chromatography. Some examples (indicated with a superscripted "a" or "b") required more than the standard 1.5 equivalents of acid chloride for the N-acylation to proceed to completion, but otherwise, all reactions were performed using the standard sets of conditions.

First, examples of the ring expansion were performed with lactams containing an ether linkage (16a) and a benzannulated system (16b), with both proceeding in good yield using the standard protocol. The high yielding synthesis of 12-membered ring 16c is an interesting case, as this shows that the ring expansion can be performed using phenol nucleophiles, whilst branched hydroxyacid derivatives are also well tolerated (16d and 16e). Also, whilst not a ring expansion reaction, the insertion of acid chloride 5b into linear amide 4m to make 16f shows that the rearrangement is not restricted to cyclic amides.

We then went on to examine successive ring expansion reactions. In total, 12 macrocyclic lactones in a range of ring sizes (14–21-membered rings) were prepared in consistently high yields via the expansion of lactams for a second time (17a–l, 61–98%), involving the installation of various combinations of α- and β-hydroxyacid derived linear fragments. We were especially pleased to discover that the new methods and products are compatible with our published lactam SuRE method; macrocycles were formed which involved the insertion of amino acid-based linear fragments in lactams before (17f,h) and after (17d,k,l) ring expansion using a hydroxy acid derivative. The ability to install both lactone and lactam motifs into the ring expanded products (in any order) is important, as this significantly increases the freedom with which functional macrocycles can be designed and prepared using the SuRE method; for example, this could have important implications for its use in the preparation of azaketolide-type antibiotics (e.g. 2 and 3, Figure 1).

We also prepared 5 macrocyclic lactones (18–24-membered rings) that demonstrate that the rings can be expanded for a third time (18a–e). Triple ring-expanded product 18a was formed in a relatively modest 36% yield, with 35% of the starting lactam 17c being recovered from the reaction due to incomplete N-acylation in this case, even after adding additional doses of acid chloride 5a. Whilst the yield in this example was somewhat disappointing, it is perhaps inevitable that there will be some variation in the efficiency of the N-acylation step, especially in larger ring systems where the conformation of the starting material may impact upon the ease with which the acid chloride approaches the lactam. Nonetheless, we were pleased that once formed, the N-acylated material underwent hydrogenolysis and ring expansion as expected, enabling the isolation of the highly oxygenated trilactone 18a. Furthermore, we were delighted to discover that the reactions proceeded more smoothly for the preparation of products 18b–e, which were formed in much higher yields (68–84%) using both α- and β-hydroxyacid derived linear fragments, and including examples which had previously been expanded with amino acid derivatives to form mixed lactam/lactone macrocycles 18c and 18e.

Finally, to further demonstrate the ease and practicality of the SuRE method, we performed the preparation of one of the triple ring expanded products (18d) without chromatographic purification at any of the intermediate stages. To help ensure complete N-acylation in each iteration, three equivalents of acid chloride 5b were used in this telescoped reaction sequence (rather than the usual 1.5 equivalents), but otherwise, no changes were made to the standard protocol other than not performing any chromatography until after the final iteration. Thus, lactam 4f was N-acylated with acid chloride 5b, and following a short aqueous work up, taken on directly to hydrogenolysis with palladium on carbon in ethyl acetate. Following this, filtration, a solvent switch (ethyl acetate to CHCl3), stirring overnight with triethylamine and aqueous work completed the first iteration. This furnished crude product 13f, which was simply reacted in the same way (to form crude 17g) and then again, to form crude 18d, which was finally purified by column chromatography and isolated in 48% overall yield over the three complete iterations (Scheme 7).

In summary, our new lactone-forming SuRE reaction system has been demonstrated in a range of high yielding ring successive ring expansion reactions. It has also been shown to be compatible with our published lactam-forming SuRE method, enabling mixed lactam and lactone-containing macrocycles using a versatile, practical protocol. Crucially, none of the methods rely on specialised reaction conditions or high dilution at any stage, with all the reactions described in this manuscript having been performed at 0.1 M concentration. Whilst all the steps in the overall SuRE process are relatively simple when considered individually (and indeed, conceptually related lactone forming ring expansion processes have been described previously),[20] we know of no other study in which such an array of complex ring expanded lactones can be assembled with the ease described in this manuscript, and none in which the ring expansion reactions can be performed iteratively. Thus, we view the relative simplicity of our SuRE method to be a key strength. The freedom to install precise sequences of lactone and lactam containing linear fragments into macrocycles in this way, and the ability to scale up the reactions if required, is expected to be of high value in the myriad scientific fields that rely on the design and synthesis of functionalised macrocycles.

**Conclusion**
Experimental Section

Full synthetic detail and spectroscopic data for all compounds are provided in the Supporting Information. General procedures A, B and C (Scheme 6) are also included below:

Procedure A

A mixture of lactam (1 mmol), DMAP (0.1 mmol) and pyridine (6 mmol) in DCM (7 mL) under an argon atmosphere was stirred at RT for 5 min. Next, a solution of acid chloride S in DCM (3.5 mL) was added, and the resulting mixture was heated, at reflux, at 50 °C for 16 h. The solvent was concentrated in vacuo, loaded onto a short silica plug and eluted with hexane:ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues, and concentrated in vacuo. This material was re-dissolved in THF (10 mL) and placed under an argon atmosphere. Palladium on carbon (100 mg, Pd 10% on carbon) and water (2 mL) was then added, and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon). The reaction was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed in vacuo. The crude material was then re-dissolved in chloroform (10 mL) and triethylamine (1.5 mmol) added, and stirred at RT for 16 h, then reduced in vacuo and purified by flash column chromatography.

Procedure B

A mixture of lactam (1 mmol), DMAP (0.1 mmol) and pyridine (6 mmol) in DCM (7 mL) under an argon atmosphere was stirred at RT for 5 min. Next, a solution of acid chloride S in DCM (3.5 mL) was added, and the resulting mixture was heated, at reflux, at 50 °C for 16 h. The solvent was concentrated in vacuo, loaded onto a short silica plug and eluted with hexane:ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues, and concentrated in vacuo. This material was re-dissolved in ethyl acetate (10 mL) and placed under an argon atmosphere. Palladium on carbon (100 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon). The reaction was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed in vacuo. The crude material was then re-dissolved in chloroform (10 mL) and triethylamine (1.5 mmol) added, and stirred at RT for 16 h, then reduced in vacuo and purified by flash column chromatography.

Procedure C

A mixture of lactam (1 mmol), DMAP (0.1 mmol) and pyridine (6 mmol) in DCM (7 mL) under an argon atmosphere was stirred at RT for 5 min. Next, a solution of acid chloride S (1.5 mmol) in DCM (3.5 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. The solvent was concentrated in vacuo, loaded onto a short silica plug and eluted with hexane:ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues, and concentrated in vacuo. This material was re-dissolved in DCM (10 mL) and placed under an argon atmosphere. DBU (10 mmol) was then added and stirred at RT for 16 h, then reduced in vacuo and purified by flash column chromatography.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: lactones · macrolides · macrolides · medium-sized rings · ring expansion

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