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Modular Synthesis of Novel Macrocycles Bearing α,β -Unsaturated Chemotypes via a Series of One-Pot, Sequential Protocols

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Abstract

A series of one-pot, sequential protocols was developed for the synthesis of novel macrocycles bearing α,β -unsaturated chemotypes. The method highlights a phosphate tether-mediated approach to establish asymmetry, and consecutive one-pot, sequential processes to access the macrocycles with minimal purification procedures. This library amenable strategy provided diverse macrocycles containing α,β -unsaturated carbon-, sulfur- or phosphorus-based warheads.

Keywords

macrocyclic compounds; one-pot reactions; heterocyclic compounds; lactams; phosphate-tether mediation

Macrocycles are privileged structures for biological studies as they can display unique features such as conformational pre-organization, flexibility, selectivity, and potential higher affinity with protein targets.^[1] Hence, macrocycles are promising molecules for the modulation of challenging processes^[2] such as protein-protein interactions^[3] and epigenetic events.^[4] Moreover, the significance of macrocycles has been demonstrated in drug development with more than one hundred macrocycle-containing compounds currently explored in therapy.^[5]

Of particular interest, naturally-occurring macrocycles bearing α,β -unsaturated entities have shown a wide range of important medicinal activities (Figure 1).^[6] In a number of cases, the presence of this type of functionality has been shown to be essential for biological activity. For instance, the *Z*-conformation provided by the conjugated lactone on microtubule binding agents laulimalide^[6d] and dictyostatin,^[6h] appears to be a necessary feature for their potent anticancer activities. Furthermore, several natural products containing α,β -unsaturated chemotypes are known to bind covalently with proteins, leading to relevant biological responses.^[7,8] Examples include the protein kinase inhibitor hypothemycin^[7a] and antibacterial agent *atrop*-abyssomicin C,^[7b] which function by covalently binding to a

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cysteine residue on their targets. Similarly, syringolin A targets the proteasome via Michael addition of a catalytic threonine to the α,β -unsaturated amide.^[7c] As a result of these contributions and others,^[8] electrophilic molecules are receiving attention in imaging,^[9] activity-based protein profiling^[10] and therapeutics,^[11] despite concerns of off-target effects.^[11c, 12]

Accordingly, natural product-based macrocycles are attractive synthesis targets that have inspired efforts in methods and libraries development.^[5a,13] Recently, we disclosed the application of one-pot, sequential operations for the concise total synthesis of α,β -unsaturated macrolactone Sch-725674 (Figure 1).^[14] By combining an uninterrupted sequence of reactions in a single flask, one-pot protocols enable the formation of multiple bonds and stereocenters in one synthetic step.^[15] This process circumvents the need for work-up and chromatography procedures between intermediary reactions with the ultimate goal of reducing time demands and waste generation. Consequently, pot-economical methods are gaining popularity^[16] as powerful strategies to achieve the synthesis of complex scaffolds while invoking atom,^[17] step,^[18] redox,^[19] and green^[20] economy. Among several featured works in the literature, elegant efforts by Hayashi^[21] are of particular note given the use of consecutive one-pot procedures to complete the multi-reaction syntheses of (–)-oseltamivir,^[22] prostaglandin A₁ and E₁ methyl esters,^[23] (–)-horsfiline and (–)-coerulescine.^[24] A later synthesis of (–)-oseltamivir^[25] was accomplished in a single pot operation and similarly, ABT-341^[26] and (*S*)-baclofen^[27] were generated following one-pot syntheses.

Inspired by these notable developments and motivated by the efficiency of our recent strategy applied to the synthesis of Sch-725674,^[14] we planned to refine the method to access diverse natural product-like, α,β -unsaturated macrolactones and surrogates. Herein, we describe the synthesis of novel macrocycles via efficient, one-pot syntheses (Scheme 1). The developed sequential protocols are amenable to the synthesis of macrocyclic libraries containing diverse α,β -unsaturated warheads, including carbon- (**1**), sulfur- (**2**) and phosphorus-based (**3**) chemotypes as electronically attenuated diversity elements. Key structural features of macrocycles **1–3** include a 14-membered ring, an unsaturated warhead, a central 1,3-*anti*-diol subunit, and a functionalized side-chain handle (Scheme 1).

Efforts to macrolactone **1a** began by employing a phosphate tether-mediated one-pot, sequential RCM/CM/chemoselective hydrogenation[“H₂”] protocol^[28] to couple phosphate triene (*R,R*)-**4** and cross-metathesis (CM) partner **5**, providing bicyclic afforded phosphate triester **6** in 40% overall yield over the course of three reactions, representing an average yield of 74% for each reaction (74% av/rxn, Scheme 2). By exploiting the orthogonal leaving and protecting group ability of bicyclic phosphate **6**, we next applied a one-pot Pd-catalyzed, reductive allylic transposition and phosphate tether removal protocol^[29g] (Scheme 2). This pot-economical operation provided 1,3-*anti*-diol **7** in 56% overall yield (83% av/rxn) after a sequence of three reactions and no solvent change. The method continued with simple protecting group manipulations and acylation with acryloyl chloride. The latter process was streamlined in a one-pot procedure and afforded acrylate ester **9a** in 75% overall yield after three reactions (91% av/rxn). The synthesis of **1a** was completed in short order via a final one-pot event consisting of a ring-closing metathesis (RCM) and

MOM-deprotection sequence in 67% yield over two reactions (82% av/rxn). Overall, 14-membered macrolactone **1a** was synthesized from triene (*R,R*)-**4** in 11.2% total yield following eleven reactions in four pots, significantly reducing intermediate isolations.

Encouraged by these results, we were next interested in exploring the applicability of our method for the generation of phosphate **6** (Scheme 1, path A).^[14,29] This first one-pot event derivatives. In particular, vinyl sulfonates and their analogs have a rich biological profile that has seen a resurgence in recent years due to their activities against enzymes involved in parasitic diseases^[30] and cancer.^[11g,31] To exploit the adaptability of the strategy, we investigated the application of the above described four-pot process for the synthesis of macrosultone **2a** (Scheme 1, path A). We were pleased to find that the protocol only required swapping acryloyl chloride with 2-chloroethanesulfonyl chloride and no alterations to the one-pot reaction conditions were necessary. Hence, the synthesis of vinyl sulfonate **10a** was accomplished via a one-pot, sequential MOM-protection/TBS-deprotection/sulfonylation operation in 72% overall yield (89.5% av/rxn, Scheme 3). Similar to **1a**, the pathway was finalized by applying a one-pot, sequential RCM/MOM-deprotection protocol, generating macrosultone **2a** in 70% yield over two reactions in one-pot (84% av/rxn, Scheme 3).

Next, we evaluated our approach for the synthesis of macrolactam (**1b**) and macrosultam (**2b**) derivatives in order to provide additional warhead diversity. On the basis of the efficiency observed during the acrylation and sulfonylation reactions in previous syntheses, we anticipated the use of similar transformations to install the corresponding amine-based, α,β -unsaturated warheads. To this end, we accommodated a one-pot procedure involving a Mitsunobu reaction on carbinol **8**, followed by azide reduction with LiAlH_4 and subsequent amine functionalization (Scheme 1, path B).

To develop this route, we investigated the use of alkaline aqueous solutions for *in situ* quenching of LiAlH_4 and successive amine functionalization. In this event, we found that saturated NaHCO_3 allows for deactivation of the reducing agent and simultaneously, provides efficient basic conditions for the addition of acryloyl chloride (Scheme 4). Following a one-pot, three-reaction procedure, the desired product **9a** was obtained in 73% yield (90% av/rxn) without any solvent adjustment. Analogously, by applying saturated K_2CO_3 and 2-chloroethanesulfonyl chloride during the third reaction of the one-pot event, sulfonamide **10b** was furnished in 81% overall yield (93% av/rxn). The corresponding macrocyclic products were then obtained via a one-pot, RCM/MOM-deprotection sequence, delivering macrolactam **1b** (60%, 77.5% av/rxn) and macrosultam **2b** (64%, 80% av/rxn, Scheme 4). Taken together, **1b** and **2b** were efficiently synthesized after a series of five one-pot operations, considerably reducing purification procedures over thirteen reaction steps from phosphate (*R,R*)-**4**.

Next, we were interested in the synthesis of related macrocycles **3a** and **3b**, given the rich biological history of phosphorus-containing molecules.^[32] The RCM precursors **11a** and **11b** were synthesized via similar processes, with the difference of carrying out the warhead installation in a separate pot due to reagent incompatibilities. Accordingly, following a two-step, one-pot sequence on intermediates **7** and **8**, and work-up, the crude product from each sequential procedure was treated with phosphorylating conditions (Scheme 5). Thus, after

three reactions in two-pots, P-chiral vinyl phosphonates **11a-R_P** and **11a-S_P** were obtained in 60% overall yield (84.5% av/rxn). Likewise, P-chiral vinyl phosphonamides **11b-R_P** and **11b-S_P** were furnished in 57% over three reactions in two-pots (83% av/rxn). In the final step, the diastereomeric mixtures underwent efficient RCM to deliver α,β -unsaturated, P-stereogenic phosphones **3a-R_P/S_P** and phosphams **3b-R_P/S_P** in 77% and 71% yields, respectively (Scheme 5). Overall, macrocycles **3a** and **3b** were accessed from (*R,R*)-**4** after conducting ten and twelve reactions, respectively, over efficient processes that reduced the number of reaction pots to five and six.

In summary, we have disclosed a series of efficient, one-pot, sequential protocols that enable the asymmetric synthesis of natural product-like macrocycles bearing an α,β -unsaturated entity (**1–3**). The macrocycles were accessed in four- to six-pot processes from (*R,R*)-**4** and fragment **5** with total yields ranging from 7.3% to 11.2%. The overall pot-economical approach is operationally simple, efficient, and library amenable. A notable merit of the method is the application of multiple consecutive pot-economic operations that significantly avoid purification procedures between successive reactions. Based on our previous applications of the RCM/CM/[“H₂”] protocol,^[29] we expect that a CM partner can be tactically chosen to assemble macrocycles with additional diversity, including various ring sizes. Further expansion of this synthetic approach for the synthesis of a variety of novel medium- and large-sized macrocycles will be reported in due course.

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Figure 1.
Bioactive macrocyclic natural products bearing α,β -unsaturated chemotypes.

Scheme 1.

Overall pot-economical approach to the synthesis of novel macrocycles bearing α,β -unsaturated chemotypes.

Scheme 2. Four-pot synthesis of α,β -unsaturated macrolactone **1a**.

Scheme 3.

Sequential one-pot protocols to α,β -unsaturated macrosultone **2a**.

Scheme 4.

One-pot protocols to α,β -unsaturated macrolactam **1b** and macrosultam **2b**.

Scheme 5.

Synthesis of α,β-unsaturated P-containing macrocycles.