

Rapid synthesis of cyclic oligomeric depsipeptides with positional, stereochemical, and macrocycle size distribution control

Suzanne M. Batiste^{a,b} and Jeffrey N. Johnston^{a,b,1}

^aDepartment of Chemistry, Vanderbilt University, Nashville, TN 37235-1822; and ^bInstitute of Chemical Biology, Vanderbilt University, Nashville, TN 37235-1822

Edited by Dale L. Boger, The Scripps Research Institute, La Jolla, CA, and approved November 20, 2016 (received for review October 4, 2016)

Macrocyclic small molecules are attractive tools in the development of sensors, new materials, and therapeutics. Within early-stage drug discovery, they are increasingly sought for their potential to interact with broad surfaces of peptidic receptors rather than within their narrow folds and pockets. Cyclization of linear small molecule precursors is a straightforward strategy to constrain conformationally mobile motifs, but forging a macrocycle bond typically becomes more difficult at larger ring sizes. We report the development of a general approach to discrete collections of oligomeric macrocyclic depsipeptides using an oligomerization/macrocyclization process governed by a series of Mitsunobu reactions of hydroxy acid monomers. Ring sizes of 18, 24, 30, and 36 are formed in a single reaction from a didepsipeptide, whereas sizes of 24, 36, and 60 result from a tetradepsipeptide. The ring-size selectivity inherent to the approach can be modulated by salt additives that enhance the formation of specific ring sizes. Use of chemical synthesis to prepare the monomers suggests broad access to functionally and stereochemically diverse collections of natural product-like oligodepsipeptide macrocycles. Two cyclodepsipeptide natural products were prepared along with numerous unnatural oligomeric congeners to provide rapid access to discrete collections of complex macrocyclic small molecules from medium (18) to large (60) ring sizes.

Mitsunobu | total synthesis | collective | macrocycle | oligomerization

Interest in the preparation and use of small molecules exhibiting macrocyclic rings is growing at a tremendous pace, driving the development of new approaches, new chemical reactions, and the underlying chemistry and tools (catalysts) to support them. Historically, studies of macrocyclization reactions have been guided by natural products bearing unusually large carbocycles or medium- and large-ring lactones, amides, and ethers. Fragmentation reactions of polycyclic molecules have long played a role in access to medium-sized macrocycles, whereas macrocyclizations to lactones and amides are often accomplished from linear precursors at high dilution. Insofar as these efforts were typically driven by the goal to prepare a specific macrocycle, often in the form relevant to a natural product synthesis or an engineered constraint to a peptide, absent from the field is an approach that provides rapid access to collections (1) of natural product-like macrocycles, particularly from stereochemically complex, functionally rich, linear precursors (2–6).

Pioneers in this area have recorded some success (Fig. 1). Esterification reactions of activated hydroxy acids have led predominantly to diolides, (7–10) and in a single case, oligolides (11). Amidation reactions of activated polypeptides were central to the preparations of macrocyclic peptides by Rothe and Kreiss (12, 13) and Wipf and coworkers (14, 15), but they were low yielding and size nonselective. Burke and coworkers (16, 17) have shown that the efficiency of an 18-membered oligolide macrocyclization can be enhanced by templation effects, but to the best of our knowledge, there is no evidence of the successful use of templation to control oligomerization/macrocyclization to produce collections of small molecules. The impact of such an approach would be further magnified by the ability

to manipulate the relative amounts of ring-size congeners within collections or even bias the process toward a single cyclic oligomer.

We sought an approach to small molecules that provides a platform for control over elements of (i) structural diversity, (ii) stereochemical diversity, and (iii) macrocycle size distribution sampled across a diverse size range. To achieve all three of these goals without compromising synthetic efficiency or relevance to complex natural products, we were attracted to cyclodepsipeptides, in which biological activity is quite diverse (18–23). Herein, we report rapid access to size-diverse collections of cyclooligodepsipeptides using a controlled oligomerization/macrocyclization sequence. A strategic combination of contemporary amide and ester preparations provides a platform for control of structural and stereochemical diversity elements, and modulation of macrocycle size distribution is possible through the use of salt additives as cyclization templates. A six-step synthesis of the natural product (–)-verticilide (1), a 24-membered macrocyclic oligodepsipeptide, in addition to its analogs ranging from 18- to 60-ring atoms displays the efficiency and simplicity with which collections of size congeners can be prepared. This approach allows access to macrocycle size congeners within cyclodepsipeptide natural product-like collections to a degree not achieved in the pioneering work with macrolides and peptidic libraries developed using dimerization and oligomerization techniques (7–17).

Results and Discussion

Verticilide (1) (Fig. 2) is a 24-membered cyclodepsipeptide isolated by Omura and coworkers in 2006 (24, 25). Its ability to selectively inhibit insect RyR led to a 14-step synthesis (24) from the (R)-oxazolidone chiral auxiliary and *N*-Me-*N*-Boc alanine.

Significance

This work resonates with the intense, rapidly broadening interest in macrocycle synthesis, enabling the preparation of collections of size-congener macrocycles in a single reaction. More specifically, we have outlined the use of the Mitsunobu reaction to forge ester linkages between hydroxy acid monomers for depsipeptides in an oligomerization/macrocyclization mode. Additionally, we disclose that salt additives, which are normally contraindicated in a Mitsunobu reaction, are able to either enhance ring-size diversity (collections) or optimize the production of one macrocycle (selection) in an ion-templated fashion. Combination of this strategy and contemporary chemical methods allows rapid access to cyclodepsipeptide natural products and their unnatural isomers.

Author contributions: S.M.B. and J.N.J. designed research; S.M.B. performed research; S.M.B. and J.N.J. analyzed data; and S.M.B. and J.N.J. wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission.

¹To whom correspondence should be addressed. Email: jeffrey.n.johnston@vanderbilt.edu.

This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1616462114/-DCSupplemental.

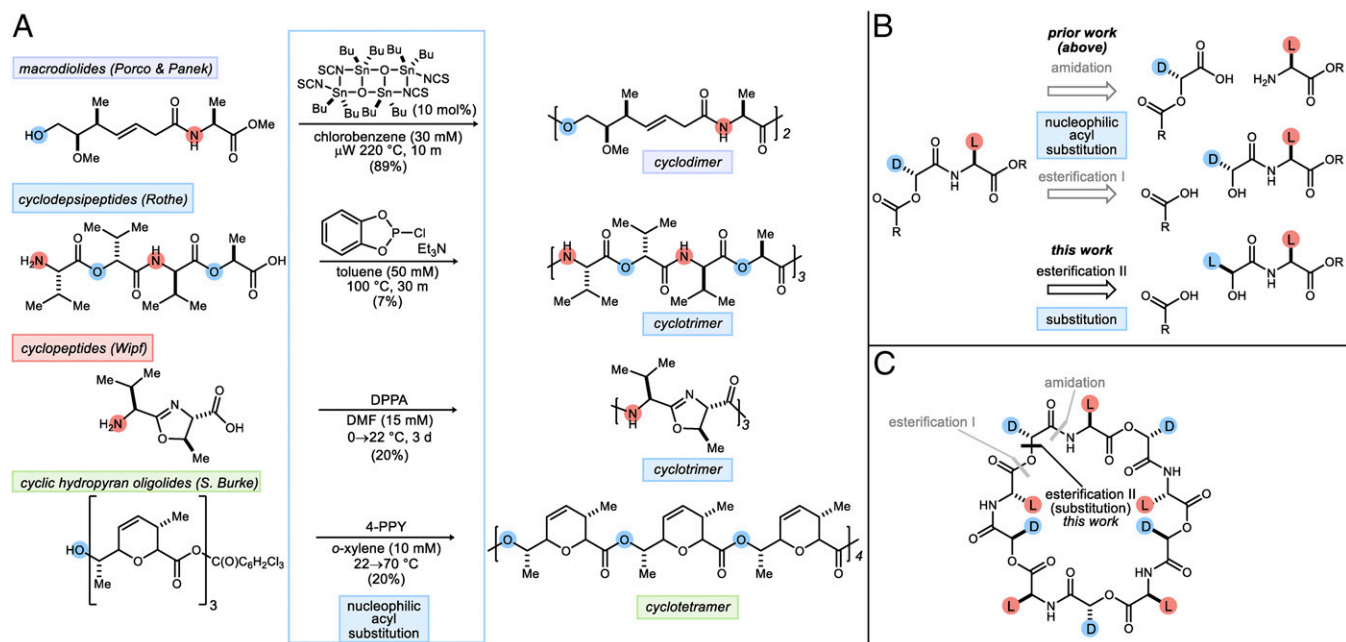


Fig. 1. (A) Combined inter-/intramolecular esterification or amidation approaches to prepare macrocycles and functional group synthesis options for depsipeptide synthesis for both (B) linear and (C) macrocycle construction.

Construction of the acyclic oligomer used PyBrop-mediated *N*-Me amide synthesis, and the final step used PyBop-mediated macrolactamization at low concentration (0.005 M) to form the remaining *N*-Me amide (Fig. 1C, amidation). An esterification approach is feasible in theory (26–29), but a drawback of esterification by nucleophilic acyl substitution is the diminished reactivity inherent to alcohol nucleophiles, especially when secondary hindered alcohols are prescribed (30) (Fig. 1C, esterification I). We instead turned to a Mitsunobu-based esterification to form the C(sp³)-O ester bond (Fig. 1C, esterification II) (31, 32) and a combination of the enantioselective Henry reaction and Umpolung Amide Synthesis (UmAS) (33) to prepare hydroxy acid didepsipeptide **5** (Scheme 1). Blay's ligand (34), conveniently synthesized in two steps from (+)-camphor, was found to provide optimal levels of enantioselectivity and yield for the copper(II) acetate-catalyzed Henry addition (35) of bromonitromethane to hexanal. Protection of the β-hydroxy-α-bromonitroalkane as its methoxymethylene (MOM) ether (**3**) was followed by UmAS with *L*-alanine benzyl ester and deprotection to hydroxy acid **5** (AlCl₃; toluene). The procedure could be performed on gram scale in 67% overall yield from hexanal.

A 20 mM solution—intentionally not high dilution—of hydroxy acid **5** in benzene was subjected to typical Mitsunobu conditions [5 equivalents (equiv) diisopropyl azodicarboxylate (DIAD) and 6 equiv triphenyl phosphine (PPh₃)] at room temperature to explore a macrocyclooligomerization (MCO) approach to verticilide. Careful analysis and purification of the reaction mixture (*SI Appendix* discusses initial findings in more detail) identified four major products, identified as cyclodepsipeptide oligomers ranging in yield from 9 to 24%. NMR analysis of these cyclooligomers revealed very similar spectra (*SI Appendix* discusses stacked NMR spectra comparison), differing primarily in the chemical shift rather than coupling pattern of each proton and reinforcing the expectation that small collections of constitutionally identical but size-distinct molecules could be prepared and purified with relative ease. The major constituent was determined to be the 36-membered congener formed in 24% yield, whereas the 24-membered macrocycle was formed in 15% yield. The 24-membered oligomer (**6**) was readily converted to natural (–)-verticilide (**1**) by straightforward amide permethylation (Scheme 1). The natural product exists as a

mixture of averaged conformational isomers in solution (¹H NMR), but the N-H precursor displays a single averaged conformer.

Although this route constituted a synthesis of verticilide in six steps with 8% overall yield, an improved yield of verticilide by MCO was sought based on the hypothesis that the growing oligomers might bind to salt additives (16, 17, 36–41), which in turn, might lead to depsipeptide–salt complexes with a conformationally enhanced rate of macrocyclization relative to chain elongation. Known applications of this phenomenon to depsipeptide macrocycle synthesis are macrolactamization (38, 39) reactions, which are conducted in a polar solvent that can readily solubilize the salt additive. However, the use of polar solvents and salt additives

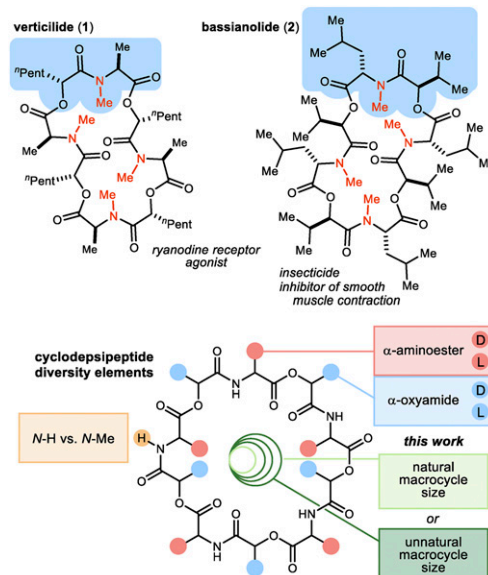
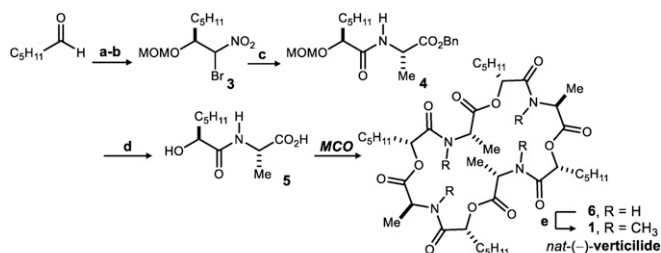


Fig. 2. Representative macrocyclic oligomeric depsipeptide natural products and diagram summarizing cyclooligomeric depsipeptide diversity elements.



(a) $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$, Blay Ligand, BrCH_2NO_2 , EtOH, -20°C , 5 d; (b) $\text{CH}_2(\text{OMe})_2$, P_2O_5 , CHCl_3 , rt, 24 h, 99% over 2 steps; (c) $\text{NH}_2\text{-(L)-Ala-O}^-\text{Bn}$, NIS, K_2CO_3 , O_2 , 2-MeTHF/ H_2O , 0°C , 2 d, 80%; (d) AlCl_3 , toluene, $0^\circ\text{C} \rightarrow \text{rt}$, 10 m, 85%; (e) NaH, MeI, DMF, 0°C , 78%.

Scheme 1. Total chemical synthesis of (natural) (-)-verticillide using MCO.

is contraindicated in a Mitsunobu reaction because of their ability to disrupt the reactive ion pairs (42–44), potentially slowing or stopping the coupling reaction entirely. Therefore, the unprecedented solubility and reactivity that we observed with the addition of various alkali metal salts (2.5 equiv) to the reaction conditions is hypothesized to be caused by an ion-templating effect between the linear depsipeptide chain and the metal ions in solution.

Fig. 3 summarizes the effect of a subset of alkali metal salts examined, with attention to those reported to bind peptides and depsipeptides in solution (45–50). Weakly coordinating counteranions were chosen for their respective alkali metal cation to promote solubility of the salt additive and interaction of the metal cation with the growing depsipeptide chain. Bromide, chloride, and tetrafluoroborate anions were chosen in particular based on their likelihood to remain inert in the reaction conditions, unlike other noncoordinating counterions (PF_6^- and ClO_4^-), which are known to form stable and insoluble complexes with arylphosphonium cations (51). Compared with the standard conditions, use of LiBF_4 and LiBr additives arrested the production of any cyclo-depsipeptide products. Lithium salts are known chaotropes, and therefore, it is not surprising that they interacted with the ionic Mitsunobu intermediates at such a level that no reactivity was observed. However, a shift in the size distribution of macrocyclic products was observed in the presence of NaBF_4 , KBF_4 , and CsCl . In the presence of NaBF_4 , KBF_4 , or CsCl , production of the 18-membered ring was completely suppressed. These three salts also provided increased amounts of 24-membered ring relative to 30-membered ring compared with providing them in nearly equal amounts without a salt additive. This effect was most significant with NaBF_4 , which provided the 24-membered ring in 25% yield as opposed to only 15% without the salt. Ring-size enhancement in the presence of a salt additive was most significant for the 36-membered ring, which was retrieved in 44% isolated yield with KBF_4 , nearly double the yield of salt-free conditions. Additionally, KBF_4 increased the overall isolated yield of macrocycles from 64 to 81% along with evidence that less material was converted into linear DIAD substrate acylation by-products. This type of by-product is common (52–54) in Mitsunobu reactions, especially in the presence of excess coupling reagents, which are generally required for a macrolactonization to occur. However, an ion template would allow the linear chain to reside in a conformation that increases the rate of cyclization relative to acylation, and the latter would be inherently slower as the linear chain increases in size. This observation supports the hypothesis that enhanced ring-size selection and overall production of macrocycles are occurring through an ion-templating effect. More notably, these results document the unprecedented ability of alkali metal salts to enhance formation of macrocycles in Mitsunobu MCO conditions.

Control over cyclodepsipeptide size (Fig. 2) can also be modulated through judicious choice of monomer length. Although dipeptide

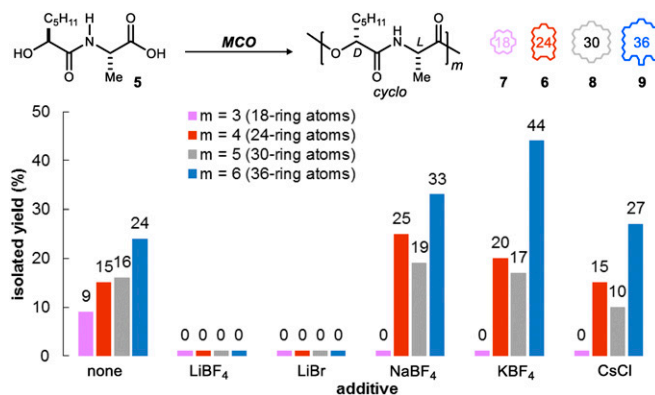
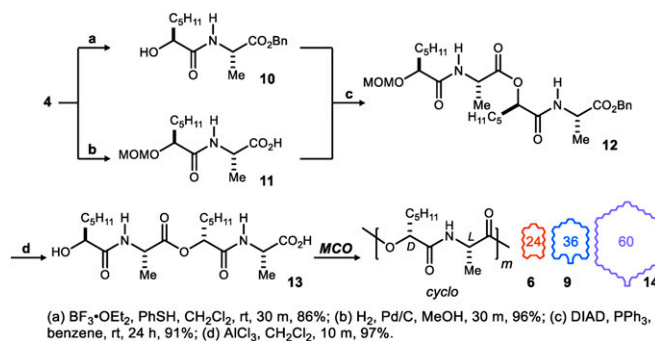


Fig. 3. Effect of salts on the production of cyclooligomers using a Mitsunobu-based oligomerization/cyclization approach and dipeptide 5.

5 provides access to oligomers that are multiples of 6-atom lengths, tetradepsipeptide **13** limits the possibilities to multiples of 12. Tetradepsipeptide **13** was prepared using a similar approach, requiring only selective deprotection of the MOM ether to **10** and the benzyl ester to produce **11** (Scheme 2). Mitsunobu coupling of these units followed by deprotection to the hydroxy acid provided **13** in 60% yield over six steps. Use of a similar oligomerization protocol led to a very different profile (*SI Appendix* discusses reaction profile in more detail) of macrocyclic oligomers (Fig. 4). Additive-free conditions led to three major products of two, three, and five units in size, corresponding to 24- (**6**), 36- (**9**), and 60-membered (**14**) rings. The 24-membered ring **6** was formed in 63% yield, whereas 36- and 60-membered cyclooligomers were formed in 10% and 5% yield, respectively. This result was particularly notable, because previously reported cyclooligomerizations of large monomers faced significant challenges with direct monomer cyclization and low overall conversion to macrocyclic products (11, 13). Because of the inherent propensity of **13** to cyclodimerize, we wondered if salt effects could make formation of the 24-membered (**6**) precursor to verticillide selective. Our previous experiments with dipeptide monomer **5** showed that this was possible to some extent when the yield of the 36-membered ring was doubled in the presence of KBF_4 .

A similar exploration of salt effects was pursued as shown in Fig. 4, but this time, the chloride versions of the tetrafluoroborate salts were tested to further examine counteranion effects. NaCl , KCl , and CsCl did not increase 24-membered ring formation. However, with increasing metal cation size, the amounts of 36- and 60-membered rings were increased. Most notably, CsCl tripled the yield of the 60-membered ring, and nearly 40% of total isolated macrocycles were larger than 24-ring atoms—results much different from salt-free conditions, where only 20% of total isolated macrocycles were greater than 24-ring atoms. As in the previous study, the most drastic



(a) $\text{BF}_3 \cdot \text{OEt}_2$, PhSH, CH_2Cl_2 , rt, 30 m, 86%; (b) H_2 , Pd/C, MeOH, 30 m, 96%; (c) DIAD, PPh_3 , benzene, rt, 24 h, 91%; (d) AlCl_3 , CH_2Cl_2 , 10 m, 97%.

Scheme 2. Synthesis of tetradepsipeptide **13** for Mitsunobu-based MCOs.

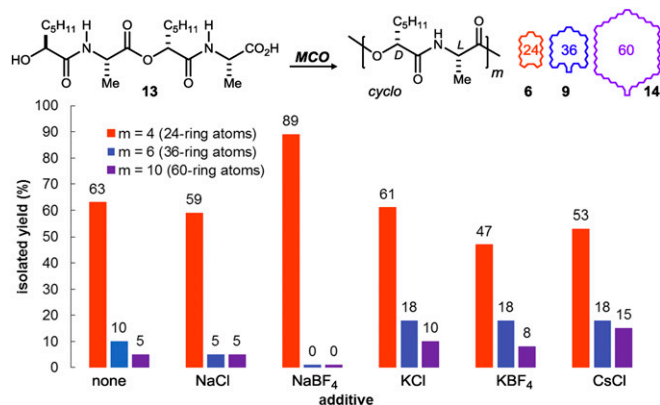


Fig. 4. Mitsunobu-based MCO of *D,L*-macrocycle progenitor tetradepsipeptide **13**: effect of salt additives on yield of 24-, 36-, and 60-membered ring formation.

templating effects were observed with tetrafluoroborate salts. Sodium tetrafluoroborate, which produced the most 24-membered ring out of all of the salt MCO conditions with monomer **5**, dramatically enhanced the formation of the 24-membered macrocycle (89% yield) and completely suppressed formation of other ring sizes with monomer **13**. Collectively, these additive effects provide a range of control that either (i) enhances diversity of oligomer size in a single reaction or (ii) enhances the formation of one macrocycle size relative to others. Contrasting approaches, the shorter preparation of verticilide results in several cyclooligomers while leveraging the didepsipeptide; use of tetradepsipeptide **13** and a salt effect that favors dimerization/macrocyclization to **6** is only slightly longer (eight steps; 36% yield).

These studies delineated the key variables that might provide controlled access to size complexity in a short step count. Insofar as enantioselective catalysis is the basis for didepsipeptide synthesis here, a broad range of precursors can be prepared. Among these precursors is the *D*-Ala epimer of **5**, because it is the progenitor to the *D,D*-cyclodepsipeptides. Monomer **15** was, therefore, prepared, and its behavior was compared with that of **5** to probe the extent to which this configuration determined the array of selectivity observed in Fig. 3. In the event, the behaviors generally paralleled those observed using the *D,L*-progenitor (**5**) (compare Fig. 3 with Fig. 5), but some differences in the cyclization of diastereomers **5** and **15** were apparent. Direct cyclization to the six-membered diketomorpholine product (38% yield) was dominant in the additive-free MCO. In general, the smaller ring

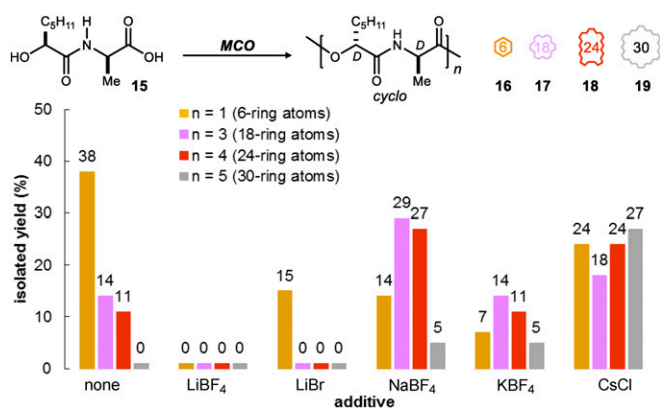
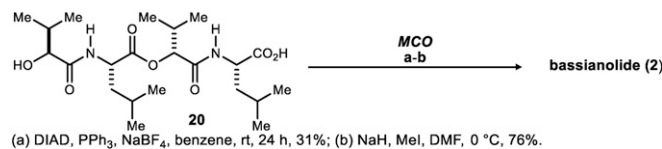


Fig. 5. Mitsunobu-based MCO of **15**: effect of salt additives on yield of 6-, 18-, 24-, and 30-membered ring formation.



Scheme 3. Synthesis of bassianolide (**2**).

sizes were most favored, forming the 18-membered macrocycle in 14% yield and the 24-membered macrocycle in 11% yield. Added salts again modified both size distribution and efficiency of MCO. Sodium tetrafluoroborate clearly enhanced the production of the higher congeners at the expense of direct cyclization to the six-membered ring. The effect of cesium chloride was also notable, because it produced a rather even distribution of four ring sizes, including a 30-membered congener that was not observed in salt-free conditions, in a combined isolated chemical yield of 93%.

The extension of this approach (Scheme 3) to a synthesis of bassianolide (**55**, **56**) (**2**) was also pursued as a means to estimate the level of generality that might be inherent to the approach and methods. Tetradepsipeptide **20** was prepared in a manner analogous to **13** and then, subjected to Mitsunobu conditions [DIAD (2 equiv), PPh₃ (3 equiv), benzene (5 mM)]. These salt-free conditions led to *N*-H bassianolide but in only 11% yield. In their synthesis of *N*-H bassianolide, Suzuki and coworkers attributed the low yield (2.8%) of their macrolactamization (PCl₅ and Et₃N) to 3₁₀-helical intramolecular hydrogen bonding (**57**, **58**) in their amino acid octadepsipeptide precursor (**59**). As a substrate for Mitsunobu esterification, **20** is a more hindered alcohol than **13**. Notwithstanding this challenge, the macrocyclodimerization of **20** was improved to 31% yield by adding NaBF₄ (5 equiv) (see *SI Appendix* for more details). Permethylation resulted in bassianolide in 9% overall yield, with an eight-step longest linear sequence.

Conclusion

In summary, a combination of enantioselective α -oxy amide synthesis and Mitsunobu-based depsipeptide synthesis provides rapid access to macrocyclic depsipeptides. Straightforward modifications of the Mitsunobu reaction through the use of salt additives can enhance the formation of size-diverse collections of macrocycles or selectivity for a single macrocycle size. A concise synthesis of the natural product verticilide grounds the work in a biologically active natural product, while providing equally straightforward access to its enantiomer and macrocyclic oligomers not yet identified in nature. Finally, bassianolide was prepared in eight steps to establish the generality of approach while highlighting the advantage of a Mitsunobu reaction-based synthesis. Attempts to develop cyclooligomerization have historically suffered from direct cyclization (12–14, **56**), favoring medium ring sizes (e.g., 12-membered depsipeptide) and competitive epimerization (15, **60**) during amide formation. The Mitsunobu substitution strategy used here provides the possibility for either the synthesis of collections of oligodepsipeptide macrocycle size congeners or the synthesis of a select ring size in high yield as well as the ability to frame-shift macrocycle size distribution by the judicious choice of monomer size (didepsipeptide vs. tetradepsipeptide). Moreover, the hybridization of enantioselective methods and UmAS provides broad access to α -oxyamide side chains without risk of epimerization during amide synthesis. The additive effects described here illustrate the potential for achieving orthogonal aims of diversity and selectivity in separate experiments and evidence of reagent control over oligomerization/cyclization. Future studies will explore this tool further, perhaps enabling higher levels of selectivity favoring large macrocycles. In this vein, the existence of large macrocyclic natural products is

notable (61, 62) as is the dearth of methods that provide rapid access to this size regime.

Supplementary Information

Procedures, complete experimental details, and analytical data for all reported compounds are provided. The

supplementary data associated with this article can be found in *SI Appendix*.

ACKNOWLEDGMENTS. Research reported in this publication was supported by National Institute of General Medical Sciences Grant NIH GM 063557.

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