A Strategy for Complex Dimer Formation When Biomimicry Fails: Total Synthesis of Ten Coccinellid Alkaloids

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ABSTRACT: Although dimeric natural products can often be synthesized in the laboratory by directly merging advanced monomers, these approaches sometimes fail, leading instead to non-natural architectures via incorrect unions. Such a situation arose during our studies of the coccinellid alkaloids, when attempts to directly dimerize Nature’s presumed monomeric precursors in a putative biomimetic sequence afforded only a non-natural analogue through improper regiocontrol. Herein, we outline a unique strategy for dimer formation that obviates these difficulties, one which rapidly constructs the coccinellid dimers psylloborine A and isopsylloborine A through a terminating sequence of two reaction cascades that generate five bonds, five rings, and four stereocenters. In addition, a common synthetic intermediate is identified which allows for the rapid, asymmetric formal or complete total syntheses of eight monomeric members of the class.

INTRODUCTION

While it is remarkable to consider the sheer wealth and architectural diversity of natural products that can be produced from a relatively small set of starting materials, equally striking is the number of structures within that collection that can be envisioned to arise via the union of a secondary metabolite with itself. Indeed, by some estimates, between 15 and 20% of all natural products likely include a dimerization process at some point in their biogenesis. This analysis includes materials with obvious symmetry, such as scetrin (1, Scheme 1), compounds with equivalent halves but non-symmetric unions, such as complanadine A (2), and materials whose symmetry has been partially erased through subsequent structural modifications like oxidation or decarboxylation, such as CP-225,917 (3). Given the significant energy invested in the creation of any natural product, the ubiquity of such dimers is logical, since dimerization enables rapid access to additional molecular scaffolds without invoking entirely new biosynthetic pathways. Indeed, with their distinct three-dimensional shapes and functional group presentations, these new materials may provide the opportunity for further creativity, as dimers distinct from those deployed by Nature can also be elaborated in tandem sequences to the final target. This concept was, to the best of our knowledge, first demonstrated by Stork in the synthesis of α-onocerin (8) in four steps from 9 and used more recently to great effect by a number of groups, including Boger in his approach to 12. It also arguably constitutes the only general solution for dimer synthesis when direct, final-step dimerization cannot be achieved, whether due to challenges in target patterning, monomer reactivity, and/or the absence of a single connecting bond to far more complex bond-forming unions, such as that postulated for the conversion of sorbicillin (4) into trichodimerol (5) through a series of Michael reactions and ketalizations. In the second dimerization approach, monomer union occurs at an earlier stage, with subsequent tandem modifications of each half leading to the final structure (as in 6 → 7 → 8 and 10 → 11 → 12). During the past several decades, synthetic chemists have become particularly skilled at utilizing both of these bio-inspired strategies to access dimeric materials from monomers.

The first strategy is the most appealing from a retrosynthetic standpoint, especially if it directly replicates Nature’s synthesis. In practice, though, it often requires extensive screening of conditions to achieve success and sometimes affords only modest yields of final product. The second approach has provided the opportunity for further creativity, as dimers distinct from those deployed by Nature can also be elaborated in tandem sequences to the final target. This concept was, to the best of our knowledge, first demonstrated by Stork in the synthesis of α-onocerin (8) in four steps from 9 and used more recently to great effect by a number of groups, including Boger in his approach to 12. It also arguably constitutes the only general solution for dimer synthesis when direct, final-step dimerization cannot be achieved, whether due to challenges in target patterning, monomer reactivity, and/or the absence of a single connecting bond to far more complex bond-forming unions, such as that postulated for the conversion of sorbicillin (4) into trichodimerol (5) through a series of Michael reactions and ketalizations. In the second dimerization approach, monomer union occurs at an earlier stage, with subsequent tandem modifications of each half leading to the final structure (as in 6 → 7 → 8 and 10 → 11 → 12).
suitable enzymes to achieve the needed bond constructions. Yet, despite their respective advantages, these two approaches also share a potential limitation: the key step linking the monomeric materials typically possesses a single reactive course. Thus, if the needed bond(s) and/or stereocenter(s) are improperly established in this operation, it is exceedingly difficult to overcome such results.

Such issues arose during our efforts to synthesize the coccinellid family of alkaloids, materials secreted by numerous species of ladybugs as defensive compounds when provoked and viewed by some as potential commercial insecticides, particularly for the control of aphid pest populations. Figure 1 provides the structures of eight of the nine monomers within this class, tricyclic architectures differing in ring junction stereochemistry, oxidation state, and olefin placement. In addition to these materials, several larger and more complex compounds are known wherein half of their framework possesses these monomer cores, such as chilocorine A as well as two other species that structurally reflect the dimeric combination of these cores in the form of psylloborine A and isopsylloborine A. The sole distinction between these latter two natural products is ring-junction enamine isomerism within their fused, highly congested, and stereochemically rich frameworks. To date, the monomeric members have elicited significant synthetic interest, with several approaches based on both classical and modern bond constructions affording every tricycle drawn in Figure 1. Intriguingly, however, it is only within the past year that the first asymmetric synthesis of any of these members has been accomplished. Equally surprising, no work toward any higher-order structure has been reported, nor has any mechanistic hypothesis been advanced to account for dimer formation in Nature.

Herein, we disclose our efforts to access this entire compound class. To date, that work has identified a single common synthetic intermediate capable of rapidly affording every monomer drawn in Figure 1. It has also led to a biosynthetic proposal for the formation of both psylloborine A and isopsylloborine A, one that, when reduced to practice, resulted in a non-natural, regioisomeric dimer. This unexpected result, coupled with observations from other instances where incorrect dimeric unions have occurred in biomimetic constructions, has led to the development of a unique, non-biomimetic strategy for complex dimer synthesis. As will be described in the ensuing sections, this alternate strategy has afforded rapid syntheses of both psylloborine A and isopsylloborine A through sequences involving some of the most complex condensation/Michael/Mannich cascade chemistry yet reported.
can likely be applied to other challenging dimerizations and may, in certain cases, be as efficient and powerful as an overall synthetic design.

## RESULTS AND DISCUSSION

### 1. Possible Biogenesis for Psylloborine A (23) and Isopsylloborine A (24).

Given the absence of any proposal for how either psylloborine A (23) or isopsylloborine A (24) might arise in Nature, we began by pondering mechanistic pathways that could account for their formation from the known tricyclic coccinellid alkaloids. The idea that ultimately proved the most attractive is shown in Scheme 2 and was inspired by a key structural observation among the monomers depicted in Figure 1. Namely, although three of those monomers (14–16) have a stable N-oxide counterpart (19–21, drawn below its respective precursor), propyleine and isopropyleine (17 and 18, a 1:3 equilibrating mixture in solution, respectively) do not. Thus, perhaps the N-oxides of 17 and/or 18 are unstable and, if generated (25), convert to a reactive electrophilic species such as 26.22 If this material was formed in the presence of a molecule of propyleine (17), then perhaps it could undergo the sequence of events shown in Scheme 2, involving a vinylogous Mannich reaction, proton transfer, Mannich reaction, and terminating proton loss to generate dimers 23 and/or 24.

In total, this proposed direct, final-stage dimerization sequence would form two new C–C bonds, one ring, and three stereocenters. The main assumption of this analysis, at least in terms of a successful laboratory execution, is that pre-existing chirality within the monomers could dictate the facial presentation of the reacting partners (i.e., enzymatic intervention would not be required). Equally critical, but unclear, were (1) whether one or both dimeric products would result from such a pathway, and (2) whether only propyleine (17) would be the active nucleophile, or if its equilibrating and more dominant enamine isomer, isopropyleine (18), could participate in addition to, or instead of, 17.

Despite these concerns, the overall attractiveness of such a dimerization process prompted us to test its viability. Thus, we set out to develop synthetic pathways to access 17/18 as well as 26.

### 2. Initial Retrosynthetic Analysis and Development of a Family-Level Approach. Scheme 3 provides a retro-synthetic approach that we hoped could ultimately address the synthetic challenges posed by the nucleophilic and electrophilic partners needed to test our proposed dimerization sequence. As
indicated, our goal was to prepare bicyclic intermediate 30 through an intramolecular condensation between the deprotected amine variant of 31 and its neighboring carbonyl. Then, if its thermodynamically favored trisubstituted enamine could be isomerized to its less stable, exocyclic counterpart and intramolecularly displace a suitably disposed leaving group, propylene (17) would result alongside its equilibrating enamine isomer, isopropyleine (18). Although isomerization to the exocyclic enamine isomer is clearly disfavored, we believed the final ring formation would be an energetically downhill and essentially irreversible process that would enable the reaction to be driven to completion.

Worth noting is that this sequence, while not fully biomimetic, is certainly bio-inspired as a disubstituted piperidine undergoing enamine condensation and subsequent attack on an intramolecular electrophile has been proposed to account for the biosynthetic formation of several monomeric alkaloids in this class.23 Indeed, as shown in the lower half of Scheme 3, Braekman and co-workers demonstrated that polyketo-myristic acid (formed from stearic acid through enzymatic oxidations) is the biosynthetic precursor to cocccinelline (19) via the proposed intermediacy of 33, a compound containing a 10-membered ring;23 the intervening steps listed above each arrow are one proposal for how these net transformations might specifically occur. Our proposed synthesis of 17/18 is based on a similar, but differently ordered, set of chemical events involving no individual ring size greater than six, in which a disubstituted piperidine (34) becomes the tricyclic system through an enamine condensation and a terminating C–C bond formation driven by nucleophilic attack of the enamine moiety.

Assuming success in our proposed synthetic operations leading to 17/18, attempts to generate electrophile 26 in situ through N-oxide formation would then begin. As an alternative approach to access 26, we also considered a de novo preparation from 32, again proposing enamine equilibration and subsequent C–C bond formation to close the final ring of its tricyclic framework. This material, in turn, we believed could also arise from 31. Given that this proposed key starting material (31) possesses three reactive domains (highlighted in blue, green, and orange) with sufficiently distinct and tunable electrophilic and nucleophilic properties, we also questioned whether another monomer configuration (i.e., 14—16 and 19—21) within the class could be accessed from the same entry point.24 If so, then a near-universal, family-level solution for the coccinellid containing a 10-membered ring;23 the intervening steps listed above each arrow are one proposal for how these net transformations might specifically occur. Our proposed synthesis of 17/18 is based on a similar, but differently ordered, set of chemical events involving no individual ring size greater than six, in which a disubstituted piperidine (34) becomes the tricyclic system through an enamine condensation and a terminating C–C bond formation driven by nucleophilic attack of the enamine moiety.

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Concurrent with these efforts, especially in light of the low-yielding Wacker oxidation step, we developed an additional sequence to 31. Though slightly longer at eight steps, it proved to be operationally simpler and higher yielding overall. It began similarly from 36, with a two-step sequence of silyl protection of the alcohol (this time as a TBS ether) and a copper-mediated addition using allylic bromide 40 that proceeded in 92% overall yield. Subsequent oxidative cleavage of the new alkene, mediated by K2OsO4 and NaIO4, afforded methyl ketone 41. The remaining carbon atoms of the target were then installed via nucleophilic addition of Grignard reagent 42, with a second oxidative cleavage then generating the ketone within 43 in 95% yield over three steps. Formation of the desired enone was accomplished via trifluoroacetate formation and DBU-induced elimination in 80% yield over two steps. Finally, the delivery of material for subsequent studies, with each being performed on relatively large scales. Indeed, the first route was able to deliver 2.68 g of 31 in a single campaign, while the second afforded 3.02 g of this key intermediate.

4. Synthesis of the Monomeric Coccinellid Alkaloids and Exploration of Dimerization Pathways to Psylloborine A (23) and Isopsyloborine A (24). With compound 31 in hand, our efforts to synthesize the monomeric members of the coccinellid class began in earnest. Starting with propyleine and isopropyleine (17 and 18, Scheme 5), we first converted the alcohol within 31 to a reactive bromide (44) through the intermediacy of its N-deprotected TFA salt (TFA; PBr3, one-pot operation). We then dissolved this material (44) in i-PrOH and treated it with Et3N in hopes that its enamine could be isomerized to its less stable, exocyclic counterpart (45) as noted earlier, thereby inducing a terminating cyclization. Pleasingly, this conjecture proved true, affording (+)-propyleine (17) and (+)-isopropyleine (18) as an equilibrating 1:3 mixture in 43% yield. This nine-step sequence to access this compound sought to dehydrate 14 in 79% yield and in 8:1 dr.

Worth noting is that both routes contributed substantively to the delivery of material for subsequent studies, with each being performed on relatively large scales. Indeed, the first route was able to deliver 2.68 g of 31 in a single campaign, while the second afforded 3.02 g of this key intermediate.

Scheme 5. Asymmetric Formal and Total Synthesis of Eight Monomeric Coccinellid Alkaloids

Reagents and conditions: (a) TFA/CH2Cl2 (1:1), 0 °C, 1 h; solvent removal, PBr3 (5.0 equiv), Et2O, 70 °C, 5 h; (b) Et3N (1.0 equiv), i-PrOH (cat.), CH2Cl2, 25 °C, 13 h, 43% yield over two steps; (c) NaBH(OAc)3 (5.0 equiv), CH2Cl2, 0 °C, 5 h, 80%, 3:7:1 dr; (d) BzONHMe-HCl (1.0 equiv), DMSO, 25 °C, 2 d, 62%; (e) TFA/CH2Cl2 (1:1), 0 °C, 1 h; concentrate, PBr3 (5.0 equiv), Et2O, 70 °C, 5 h; (f) Et3N(0.77 equiv), i-PrOH (0.91 equiv), CH2Cl2, 40 °C, 4 h; concentrate, aq NaOH (10 equiv), MeOH, 65 °C, 6 h, 46% over two steps, 1:1.2 dr, recyclable.

its N-oxide congener coccinelline (19, cf. Figure 1).198 its preparation allowed us to claim a formal synthesis of this oxidized monomer as well.

Alternatively, α-oxidation of common intermediate 31 with BzONHMe-HCl,30 followed by the same general steps already described (TFA; PBr3 in one pot then Et3N, i-PrOH; NaOH) generated oxidized skeleton 48 by way of 47 as a mixture of recyclable diastereomers about the new, highlighted chiral center.31,32 This compound (48) has previously been advanced by Mueller to hippocamine and hippocasine (15 and 16, respectively) as well as their N-oxides (20 and 21, cf. Figure 1),15g,33 thus completing total and/or formal syntheses of all eight monomers drawn in Scheme 1, all starting from a single starting material (i.e., 31).

With syntheses of our targeted monomers complete, our attention now turned to dimerization. Although our proposed nuleophilic partner was already available from the synthesis of propyleine and isopropyleine (17 and 18), efforts to generate a reactive electrophile directly from these materials through N-oxidation were unsuccessful. As such, we sought an alternate and potentially more controlled path to the needed electrophilic dimerization precursor in the form of cross-conjugated diene 49 (Scheme 6). Our hope was that, upon exposure to an appropriate proton source, iminium electrophile 26 (Schemes 2 and 7) could be generated in situ, and then we could expose that species to the appropriate nuleophilic partners. Our initial route to access this compound sought to dehydrate 51, itself

Scheme 6. Preparation of Key Dimerization Precursor 49 from Key Intermediate 31

Reagents and conditions: (a) (COCl)₂ (1.6 equiv), DMSO (3.2 equiv), Et₃N (6.0 equiv), CH₂Cl₂, −78 °C to 0 °C, 90 min, 94%; (b) TFA/CH₂Cl₂ (1/1), 0 °C, 1 h, carried forward crude; (c) RuO₂⋅H₂O (0.10 equiv), acetone/H₂O (1:1), 0 °C, 90 min, 77%; (d) p-nitrophenol (1.2 equiv), DCC (1.2 equiv), 4-DMAP (0.10 equiv), 25 °C, 20 h; filter, solvent removal, TFA/CH₂Cl₂ (1:1), 0 °C, 1 h; (e) i-PrOH (cat.), CH₂Cl₂, 40 °C, 18 h, 31% over two steps; (f) DIBAL-H (2.5 equiv), THF/1,4-dioxane (4:1), 25 °C, 4 min.

Scheme 7. Attempts at Direct, Late-Stage Dimerization Led to a Non-natural Dimeric Analogue (54) with Incorrect Regiocontrol

Reagents and conditions: (a) TFA (1.0 equiv based on vinylogous amide 53), 25 °C, 2 min; 17 and 18 (1:3, 1.07 equiv combined based on vinylogous amide 53), 25 °C, 2 h, 21% over two steps.

Figure 2. Possible basis for the observed dimerization result based on transition-state models for electrophile addition (i.e., 26) using either the propyleine (17) or isopropyleine (18) enamine as nucleophile.
on a conceptually different approach for dimer synthesis from those posited within the confines of Scheme 1 and centered on the long-established principle that intramolecular dimerization can potentially overcome those factors governing intermolecular reactivity. Specifically, rather than combine advanced materials in a final step or merge simpler materials earlier and then elaborate in tandem, instead (1) link two simpler precursors at an appropriate site to ensure proper regiocontrol and (2) embed enough chiral information and reactivity within the overall structure to establish the remaining rings and stereocenters as well as forge any remaining bonds between the two halves.

We term this approach "intramolecular dimerization," and compound 59 was designed for the coccinellid alkaloids on the basis of its general concepts, outfitted with one of the requisite dimer linkages (highlighted in purple in Scheme 8) that could not be forged from direct, advanced monomer coupling. From here, two cascades were envisioned to forge the remaining rings, stereocenters, and final dimeric linkage needed to complete the targets. Initiation of the first cascade required the ability to differentiate selectively between the protecting groups on the two piperidine rings in 59 to reach 58 via a condensation and Michael closure. The second cascade would utilize an added electron-withdrawing group (EWG, colored in blue) on one of the pendant methyl groups of the final target to dictate the correct order of bond constructions through condensation, enamine-based Michael attack to form the tricyclic ring system, and a terminating Mannich ring-closure to complete the carbon framework. Collectively, these two cascades would forge five new bonds, five new rings, and four stereogenic centers, assuming again that pre-existing chirality within 59 could govern the incorporation of the remaining chiral elements. If successful, then a terminating excision of the EWG in cascade product 57 would complete the synthesis of 23 and/or 24.

On initial inspection, this approach appears contrary to the general tenets of retrosynthetic analysis, since an arguably more complex precursor and set of terminating events are required than those needed for the two dimerization strategies presented in Scheme 1. However, given the failure of direct dimerization and the likely inapplicability of tandem elaboration to a non-symmetric dimer, we required a distinct strategy. One potential and logical benefit of this new approach is that the final stitching operations appear to take advantage of biosynthetic efficiency through the use of cascades that resemble Nature’s synthesis of the monomeric frameworks. Indeed, apart from the linkage within 59, the portions of this material colored in Scheme 8 match very closely the analogous portions of structures 55 and 56, moving only one bond colored in black and changing the positioning and identity of the functional groups colored in blue. Moreover, we anticipated that this synthetic sequence would not be much longer than the failed direct dimerization strategy. Indeed, key test substrate 59 was expected to readily arise from a Horner–Wadsworth–Emmons coupling between phosphonate 60, a material we anticipated could be readily synthesized, and aldehyde 50, the oxidized version of our key common intermediate for monomer synthesis which was already available on gram scale (cf. Scheme 6). For maximal flexibility in EWG selection, the incorporation of this group would be attempted once most of 59 had been assembled to afford opportunities to probe different variants as needed to successfully induce the designed cascades.

As shown in Scheme 9, the key elements of this new "dimerization" precursor were indeed synthesized quite readily, starting once again from piperidine 36, the same material used earlier to commence our monomer syntheses. Its core elements closely mirror the synthetic pathways described earlier in the context of Scheme 4, differing only in terms of the fragments coupled, and thus will not be discussed in detail (Scheme 9). Pleasingly, after phosphonate 60 was accessed in just six steps from 36, the Masamune–Roush variant of the Horner–Wadsworth–Emmons reaction (LiCl, i-Pr2NEt in CH3CN at 25 °C) coupled it with aldehyde 50 to afford 65, with the previously inaccessible intramolecular dimerization linkage now in place (highlighted in purple in Scheme 9).

From here, treatment of 65 (Scheme 10) with TFA at −78 °C differentiated the two Boc-protected piperidine ring systems by taking advantage of neighboring group participation, selectively transforming the upper ring Boc group (as drawn) into a base-labile carbamate through cyclization onto the enone while leaving the lower ring Boc group intact. Although this operation afforded no stereocontrol at the highlighted center.
Scheme 9. Synthesis of Key Linking Bond as a Prelude to Testing the Designed Closure Cascades for Psylloborine A and Isopsylloborine A Synthesis

“Reagents and conditions: (a) TBSCI (1.1 equiv), imidazole (2.0 equiv), CH₂Cl₂, 25 °C, 19 h; (b) sec-BuLi (1.5 equiv), CuCN, allylBr, THF, −78 °C to −45 °C, 1 h; CuCN-2LiCl (1.5 equiv), −78 °C, 1 h; allyl bromide (5.0 equiv), −78 to 25 °C, 2 h, 91% over two steps; (c) K₂OsO₄·2H₂O (0.005 equiv), NaIO₄ (4.0 equiv), 2,6-lutidine (2.0 equiv), 1,4-dioxane/H₂O (3/1), 25 °C, 25 min, 79%; (d) CuCN (1.0 equiv), 25 °C, 4 h; HCl (6.0 equiv), MeOH, 0 °C, 25 min, 79%.

Within 66, that outcome was of no consequence, as this chiral center would be subsequently destroyed. The synthesis of the key precursor (in protected form as 66) was then completed by oxidizing the alcohol and performing a Horner–Wadsworth–Emmons coupling with an aryl sulfone-containing phosphonate [either Ph-, 3,5-(CF₃)₂Ph-, or 4-NO₂Ph-, vide infra].

The stage was now set for the first critical cascade. Pleasingly, treatment of all three of these variants of 66 with 1,1,3,3-tetramethyldiamine (TMG) in a 9:1 mixture of toluene/i-PrOH effected the desired reaction sequence of carbamate cleavage, enone regeneration, condensation, enamine equilibration to the exocyclic isomer, and a terminating Michael addition. However, despite the high control in bond construction events, the highlighted chiral center within 68 was generated in a 1:1.2 dr favoring the undesired, undrawn epimer. Exploration of various conditions revealed that this outcome could not be improved, with several alternatives affording inferior stereoselection. While not optimal, it was certainly an improvement on the direct dimerization approach where that center could not be forged correctly to any degree.

Pressing forward with both diastereomers (as they could not be separated at this stage when the EWG was an aryl sulfone), treatment of 68 with TFA in CH₂Cl₂ at 0 °C for 1 h removed the remaining Boc group to unveil the free amine needed to initiate the second cascade. Subsequent dissolution in benzene-i-PrOH (9:1), 25 °C, 1.5 h, 87%; (g) LiCl (4.0 equiv), i-Pr₂NEt (2.0 equiv), 25 °C, 30 min; 50 (1.0 equiv), 25 °C, 4 h; HCl (6.0 equiv), MeOH, 0 °C, 25 min, 79%.

Scheme 10. Total Synthesis of Psylloborine A (23) and Isopsylloborine A (24) via the “Intramolecular Dimerization” Strategy

“Reagents and conditions: (a) 10% v/v TFA in CH₂Cl₂ (10 equiv), CH₂Cl₂, −78 °C, 2 h, 89%, 2:1 dr; (b) oxalyl chloride (1.6 equiv), DMSO (3.2 equiv), Et₃N (6.0 equiv), −78 °C, 30 min; 0 °C, 1 h; (c) phosphate (Ar = 3,5-(CF₃)₂Ph-, 1.0 equiv), LiCl (2.0 equiv), i-Pr₂NEt (2.0 equiv), CH₂CN, 25 °C, 30 min; substrate (1.0 equiv), CH₂CN, 25 °C, 2 h, 67% over two steps (all ensuing yields are for when Ar = 3,5-(CF₃)₂Ph-); (d) TMG (1.0 equiv), toluene/i-PrOH (9:1), 25 °C, 5.5 h, 1:1.2 dr; (e) TFA/CH₂Cl₂, 0 °C, 1 h; (f) C₂D₆, 65 °C, 3 h, 15% yield over three steps (79% yield per transformation); (g) 5 wt % Na/Hg (276 equiv), i-PrOH, 25 °C, 30 min, 46%; (h) TFA (2.0 equiv), CH₂Cl₂, 75 °C, 30 min, ∼75%.

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chemistry yet described, given that they involve a total of seven distinct chemical events that forged three C–C bonds, two C–N bonds, five rings, and four stereocenters; the overall yield obtained for the 3,5-(CF$_3$)$_2$Ph variant, at 15%, reflects a throughput of 79% per chemical transformation. Finally, exposure of the 3,5-(CF$_3$)$_2$Ph derivative of 72 to Na/Hg amalgam$^{23}$ transformed it into psylloborine A (23), a material identical in all respects to the natural isolate, thereby completing the first total synthesis of this molecule as well as that of any dimeric coccinellid alkaloid.$^{43}$ As a final experiment, heating this material with TFA in CICH$_2$CH$_2$Cl at 75 °C afforded isopsylloborine A (24), completing the first total synthesis of this dimer as well as establishing 23 as a viable biosynthetic precursor to 24.$^{44}$ In total, the route to 23 required 16 linear steps, only four steps more than the original direct dimerization approach that failed to deliver the target, thus highlighting the efficiency of this alternate dimerization strategy.

Finally, it is worth noting that while only the 3,5-(CF$_3$)$_2$PhSO$_2$- group afforded complete success for the entire sequence, EWGs other than sulfones were also probed for the failed terminating ring-closure.$^{45}$ Collectively, these findings reveal overall that, while there is some flexibility in the groups that can allow the key elements of this cascade chemistry to proceed, careful control of electronics is required to fully orchestrate the designed sequences.

**CONCLUSION**

In summary, a concise synthesis of ten members of the coccinellid family of alkaloids has been accomplished in both total and formal format, all starting from a single, common intermediate. Key components of the developed chemistry include the use of several cascade-based bond constructions involving finely tuned and highly reactive intermediates coupled with a new synthetic logic for the formation of dimeric natural products where biomimetic, direct dimerization approaches have failed to control regio- and stereoselectivity. We anticipate that this unique design for dimerization is applicable to a number of other natural product compound classes, foremost of which may be the myrmicarin alkaloids for which available approaches have failed. Work is ongoing to verify that assertion, as are biochemical studies of the synthesized materials and efforts to prepare other molecules in the class.

**ASSOCIATED CONTENT**

* Supporting Information
  Detailed experimental procedures, copies of all spectral data, and full characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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**Notes**

The authors declare no competing financial interest.

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(9) For a recent example in a highly complex scenario, see: (a) Herzon, S. B.; Schwinger, H.; Lin, Y.; Zografos, A. L. J. Am. Chem. Soc. 2009, 131, 1753.


(10) For a recent review on cascade reactions in natural product total synthesis, see: Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. Angew. Chem., Int. Ed. 2006, 45, 7134.

(12) In principle, such a species could also result without the intermediary of an N-oxide through alternate oxidative pathways involving the enamine of 18.


(38) A tandem strategy, while elegant, is less applicable to these coccinellid dimers, as they are pseudosymmetric and the monomeric components are of differing oxidation state. Some initial attempts were made to investigate pseudo-tandem closure cascades on fully deprotected analogues of 66 and close structural congeners; however, these efforts were unsuccessful in delivering materials resembling 72, thereby strengthening the need to utilize an alternative approach delineated with stepwise polycycle constructions.
(41) Trace amounts of 72 did form. The structure assignment of 71, as noted, is tentative, with its instability precluding full characterization. However, the data obtained are of high homology to the fully characterized 75 introduced in the context of Scheme 11. We also note that the undesired diastereomer of 68 which was carried into this final cascade sequence formed uncharacterized products that were separated from the desired polycycles once those operations were complete.
(43) The 4-NO₂PhSO₂ variant of 72 (formed in 12% yield from 66, 77% yield per transformation) formed the aniline first, and then decomposed under more forcing reaction conditions.
(44) The spectra of psylloborine A (23) were compared directly to physical spectra of the natural source. Efforts to obtain similar spectra for 24 were not successful. Notably, it appears that 24 was originally characterized (ref 18) as a partial salt with an unspecified stoichiometry of TFA added to the sample. We have attempted to reproduce these conditions and have also fully characterized the mono-TFA salt of 24 via 2D NMR spectroscopy. See the Supporting Information for full details.
(45) The EWG handles do undergo Michael additions on simpler systems, bolstering the idea that in this more complex system the cascade electronics must be finely tuned.