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

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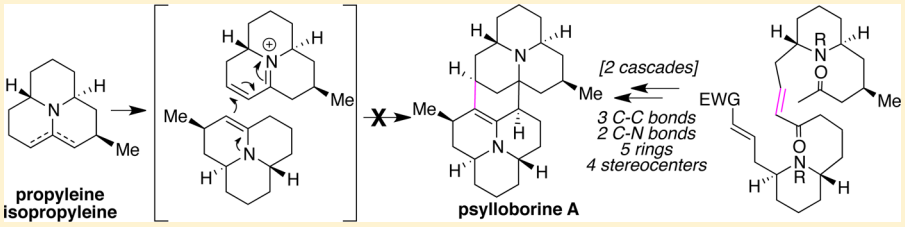
Supporting Information



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.[1] This analysis includes materials with obvious symmetry, such as sceptrin (**1**, Scheme 1),[2] compounds with equivalent halves but non-symmetric unions, such as complanadine A (**2**),[3] and materials whose symmetry has been partially erased through subsequent structural modifications like oxidation or decarboxylation, such as CP-225,917 (**3**).[4] 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 well afford evolutionary advantages to the producing species.[5]

Considering only those dimeric natural products that possess obvious monomer symmetry (i.e., those that have not undergone extensive modifications, such as **3**), Nature appears to deploy two general strategies to access such materials. The first and most typical approach forges the dimer in a final synthetic operation from fully functionalized monomers. Such processes can range from the simple and direct construction 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.[6] 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**).[7]

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.[8] The first strategy is the most appealing from a retrosynthetic standpoint, especially if it directly replicates Nature's synthesis.[9] 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**,[10] and used more recently to great effect by a number of groups,[11] including Boger in his approach to **12**.[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

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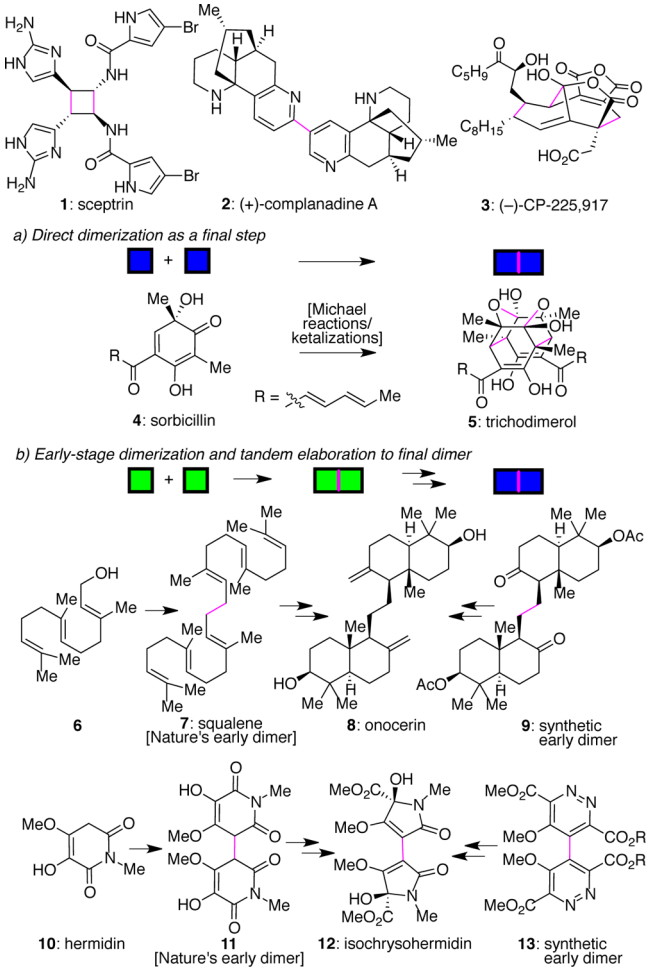
Scheme 1. Ubiquity of Dimers in Nature and Available Strategies for Their Formation in Nature and in the Laboratory[a]



[a]Dimer linkages are colored in purple.

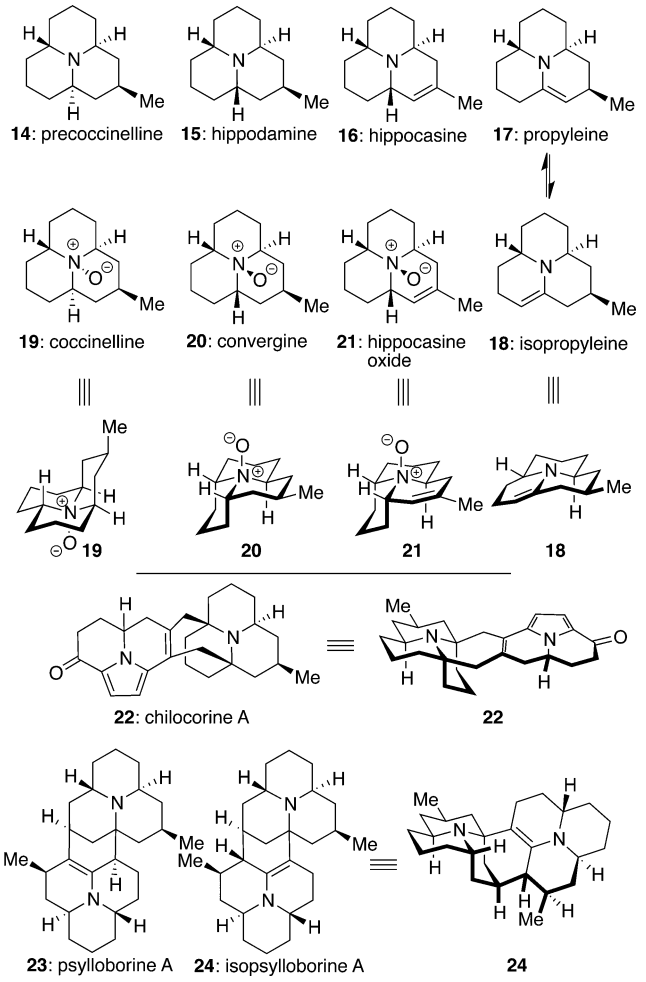


Figure 1. Structures of the coccinellid class of alkaloids: unique monomeric and dimeric frameworks.

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[13] and viewed by some as potential commercial insecticides, particularly for the control of aphid pest populations.[14] Figure 1 provides the structures of eight of the nine monomers within this class (**14**–**21**), tricyclic architectures differing in ring junction stereochemistry, oxidation state, and olefin placement.[15]

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 (**22**),[16] as well as two other species that structurally reflect the dimeric combination of these cores in the form of psylloborine A (**23**)[17] and isopsylloborine A (**24**).[18] 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.[15g,19] Intriguingly, however, it is only within the past year that the first asymmetric synthesis of any of these members has been accomplished.[19i] 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.[20] It has also led to a biosynthetic proposal for the formation of both psylloborine A (**23**) and isopsylloborine A (**24**), 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 (**23**) and isopsylloborine A (**24**) through sequences involving some of the most complex condensation/Michael/Mannich cascade chemistry yet reported.[21] Significantly, this approach

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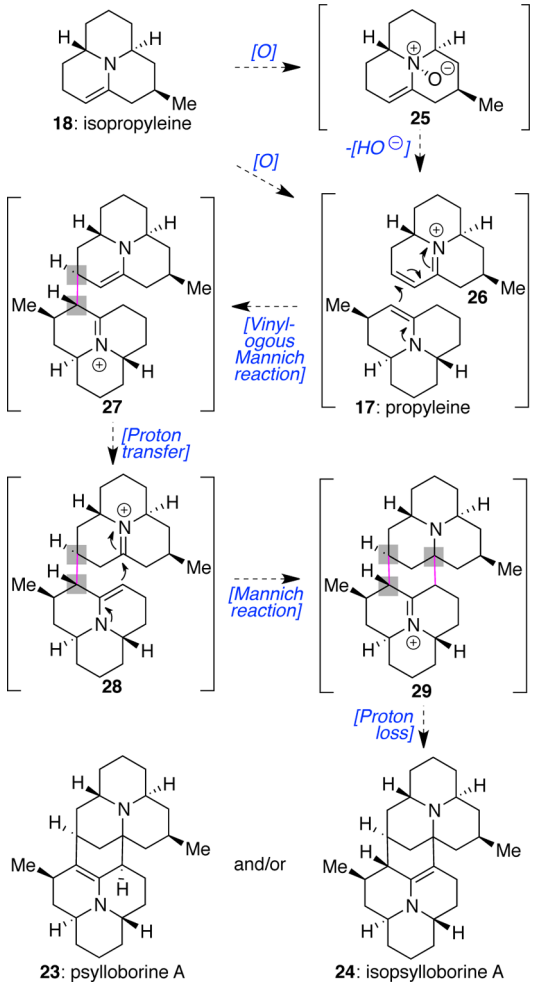
can likely be applied to other challenging dimerizations and may, in certain cases, be as efficient and powerful as an overall synthetic design.

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

Scheme 2. Proposed Biogenesis of Psylloborine A (23) and Isopsylloborine A (24) via Oxidation of Isopropyleine (18)



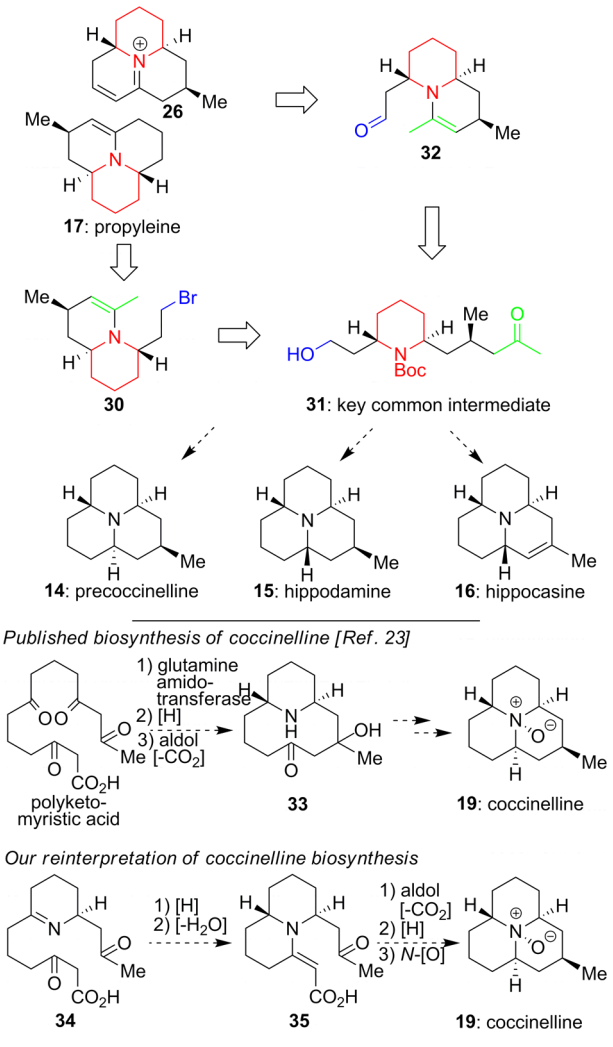
inspired by a key structural observation among the monomers depicted in Figure 1. Namely, although three of those monomers (**14**–**16**) have a stable *N*-oxide counterpart (**19**–**21**, drawn below its respective precursor), propyleine and isopropyleine (**17** and **18**, a 1:3 equilibrating mixture in solution, respectively)[15g] 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 retrosynthetic 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

Scheme 3. Global Retrosynthetic Analysis for the Monomeric Coccinellid Alkaloids from Key Intermediate 31



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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, propyleine (**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.

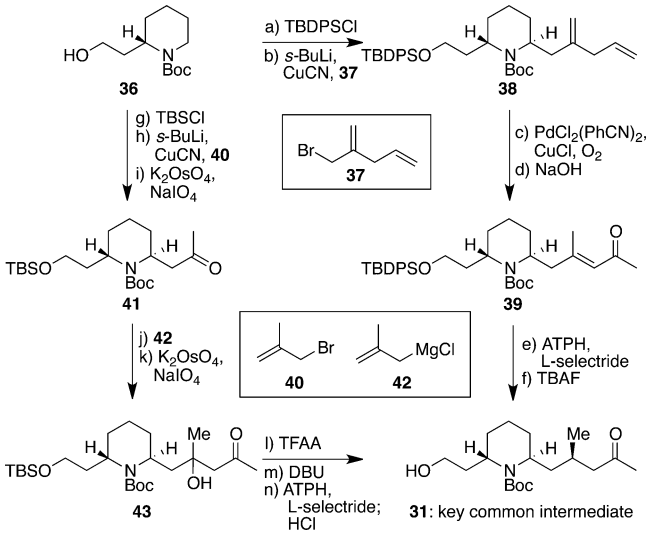
Worth noting is that this sequence, while not fully biomimetic, is certainly bio-inspired as a disubstituted piperidine undergoing enamine condensation and subsequent attack on an intramolecular electrophile has been proposed to account for the biosynthetic formation of several monomeric alkaloids in 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 coccinelline (**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 every other 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 alkaloids would exist, with enantioselective syntheses of all monomeric members possessing optical activity being achieved, some for the first time.

3. Synthesis of Key Building Block 31. Based on this plan, our first objective was to devise an efficient synthesis of our key, common building block (**31**). As shown in Scheme 4, we ultimately developed two different routes to accomplish that goal, both starting from the commercially available *N*-Boc-(*S*)-(−)-piperidine-2-ethanol (**36**). This material was chosen because it possessed a key chiral center that we anticipated would readily encode the remaining stereochemical information into the final target.

Our first route began with silylation of the alcohol and was followed by a copper-mediated allylation with branched bromide **37**,[25] itself available in two steps from propargyl alcohol (see Supporting Information for synthesis). These operations led to *trans*-disposed intermediate **38** in 84% overall yield and with >19:1 diastereoselectivity based on ^{1}H NMR

Scheme 4. Synthesis of Key Intermediate 31 via Two Different Routes[a]



[a]Reagents and conditions: (a) TBDPSCl (1.05 equiv), imidazole (2.0 equiv), CH_2Cl_2, 25 °C, 19 h; (b) *s*-BuLi (1.5 equiv), TMEDA (1.6 equiv), Et_2O, −78 to −45 °C, 1 h; CuCN·2LiCl (1.5 equiv), −78 °C, 1 h; **37** (3.0 equiv), −78 to 25 °C, 4 h, 84% over two steps; (c) $PdCl_2(PhCN)_2$ (0.1 equiv), CuCl (1.0 equiv), DMF/H_2O (10/1), O_2, 60 °C, 6 h, 41%; (d) NaOH (2.0 equiv), *i*-PrOH, 25 °C, 1 h, 100%; (e) ATPH (1.5 equiv), CH_2Cl_2, 0 °C, 20 min; L-Selectride (2.0 equiv), −78 °C, 1 h, 75%, 15:1 dr; (f) TBAF (2.0 equiv), THF, 25 °C, 2 h, 91%; (g) TBSCl (1.1 equiv), imidazole (2.0 equiv), CH_2Cl_2, 25 °C, 19 h; (h) same as step b but with **40** (5.0 equiv) instead of **37**, 92%; (i) $K_2OsO_4·2H_2O$ (0.005 equiv), $NaIO_4$ (4.0 equiv), 2,6-lutidine (2.0 equiv), 1,4-dioxane/H_2O (3/1), 25 °C, 24 h; (j) **42** (2.2 equiv), THF, −78 °C, 2.5 h; (k) $K_2OsO_4·2H_2O$ (0.005 equiv), $NaIO_4$ (4.0 equiv), 2,6-lutidine (2.0 equiv), 1,4-dioxane/H_2O (3/1), 25 °C, 16 h, 95%; (l) TFAA (5.0 equiv), pyridine (15 equiv), 4-DMAP (0.1 equiv), CH_2Cl_2, 0 °C, 1.5 h; (m) DBU (1.5 equiv), CH_2Cl_2, 0 to 25 °C, 1.5 h, 80% (n) ATPH (1.5 equiv), CH_2Cl_2, 0 °C, 30 min; L-Selectride (2.0 equiv), −78 °C, 1 h; 1 M HCl (10 equiv), MeOH, 25 °C, 1 h, 79%.

analysis.[26] With all of the carbons of the final target already in place, only functional group manipulations and redox adjustments remained. These events began by conversion of **38** into enone **39** through a modestly yielding and sometimes capricious Wacker oxidation (41% yield) promoted by $PdCl_2(PhCN)_2$ in DMF/H_2O at 60 °C, followed by a nearly quantitative base-induced (NaOH) olefin isomerization; these transformations afforded the new alkene with 4:1 selectivity which we assume to have the structure shown, though we never explicitly confirmed the process as being *E*-dominant. Next, we hoped to set the methyl stereocenter of the target through a diastereoselective reduction. This step ultimately proved to be the most challenging of the sequence, with repeated attempts at substrate-directed hydrogenation using Wilkinson's or Crabtree's catalysts affording either no diastereoselection or preference for the undesired methyl epimer on **39** or its deconjugated enone precursor. Fortunately, use of Yamamoto's bulky Lewis acid, aluminum tris(2,6-diphenylphenoxide) (ATPH),[27] in tandem with L-Selectride afforded the desired stereocenter with a 15:1 diastereomeric ratio (dr) and in 75% yield.[28] A final desilylation using TBAF in THF at 25 °C then delivered the desired building block (**31**) in a sequence that was just seven steps overall (including the two-step preparation of **37**).

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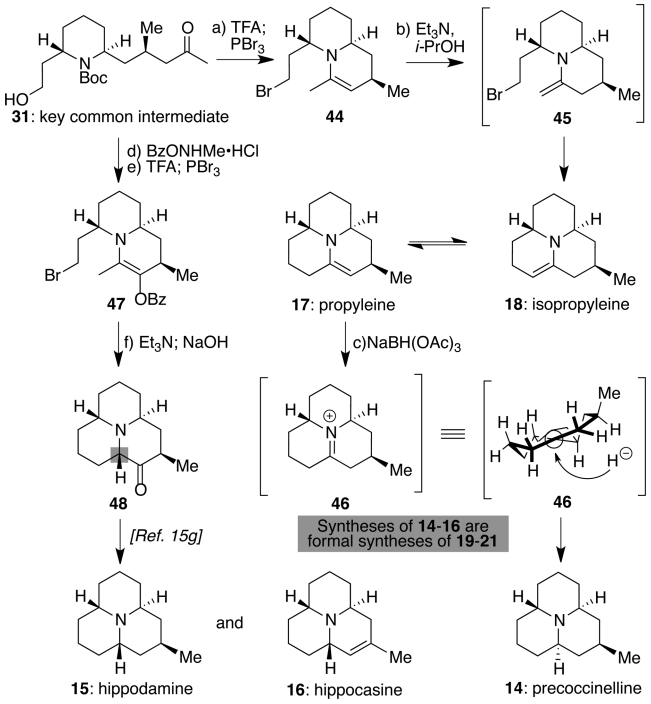
Concurrent with these efforts, especially in light of the low-yielding Wacker oxidation step, we developed an additional sequence to **31**. Though slightly longer at eight steps, it proved to be operationally simpler and higher yielding overall. It began similarly from **36**, with a two-step sequence 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 K_2OsO_4 and $NaIO_4$,[29] 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, this transformation was followed by the same facially selective hydride delivery, with a terminating *in situ* deprotection upon quenching of the [1,4]-reduction product with HCl, completing the synthesis of **31** 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.

4. Synthesis of the Monomeric Coccinellid Alkaloids and Exploration of Dimerization Pathways to Psylloborine A (23) and Isopsylloborine 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; PBr_3, one-pot operation). We then dissolved this material (**44**) in *i*-PrOH and treated it with Et_3N 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 (using the step count of the shorter route to **31**) is the first asymmetric solution for these targets and the shortest route to date. In addition, the levorotatory rotation of the final synthetic materials matched that of the natural isolates, confirming the absolute configuration of these compounds for the first time as based on the initial assignment of **36** (cf. Scheme 4).

From here, subsequent reduction of a portion of these natural products with $NaBH(OAc)_3$ led to a 3.7:1 mixture of precoccinelline (**14**) and hippodamine (**15**, Scheme 5). Due to the *trans*-ring fusions of these materials, it was difficult to predict the outcome of this reaction *a priori*. However, given the observed facial bias, we presume that if the top ring (as drawn in the two-dimensional depiction of **46**) were to adopt a twist-boat orientation, as indicated by the three-dimensional representation of imine **46** in Scheme 5, then hydride delivery from the bottom face would appear to be preferred, forming precoccinelline (**14**). If true, then hippodamine (**15**) would have resulted from hydride delivery onto the other side of the structure. Presumably, delivery from the top face, forming hippodamine, forces the methyl group into an unfavorable 1,3-diaxial relationship with the incoming hydride in the transition state, whereas delivery from the opposite face produces no such interaction. From the standpoint of synthesis, however, as precoccinelline (**14**) has previously been readily converted into its *N*-oxide congener coccinelline (**19**, cf. Figure 1),[19g] its preparation allowed us to claim a formal synthesis of this oxidized monomer as well.

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



[a]Reagents and conditions: (a) TFA/CH_2Cl_2 (1:1), 0 °C, 1 h; solvent removal, PBr_3 (5.0 equiv), Et_2O, 70 °C, 5 h; (b) Et_3N (1.0 equiv), *i*-PrOH (cat.), CH_2Cl_2, 25 °C, 13 h, 43% yield over two steps; (c) $NaBH(OAc)_3$ (5.0 equiv), CH_2Cl_2, 0 °C, 3 h, 80%, 3.7:1 dr; (d) BzONHMe·HCl (1.0 equiv), DMSO, 25 °C, 2 d, 62%; (e) TFA/CH_2Cl_2 (1:1), 0 °C, 1 h; concentrate, PBr_3 (5.0 equiv), Et_2O, 70 °C, 5 h; (f) Et_3N (0.77 equiv), *i*-PrOH (0.91 equiv), CH_2Cl_2, 40 °C, 4 h; concentrate, aq NaOH (10 equiv), MeOH, 65 °C, 6 h, 46% over two steps, 1:1.2 dr, recyclable.

Alternatively, α-oxidation of common intermediate **31** with BzONHMe·HCl,[30] followed by the same general steps already described (TFA; PBr_3 in one pot then Et_3N, *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 hippodamine 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 nucleophilic 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 nucleophilic partners. Our initial route to access this compound sought to dehydrate **51**, itself

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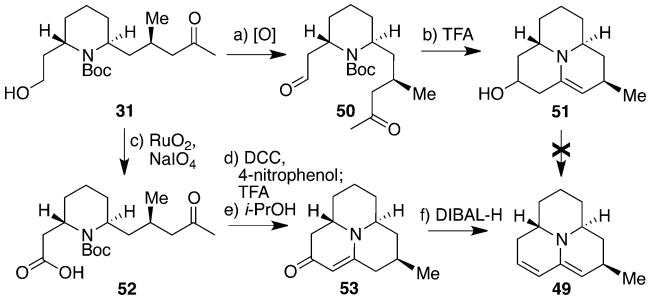
Scheme 6. Preparation of Key Dimerization Precursor 49 from Key Intermediate 31[a]



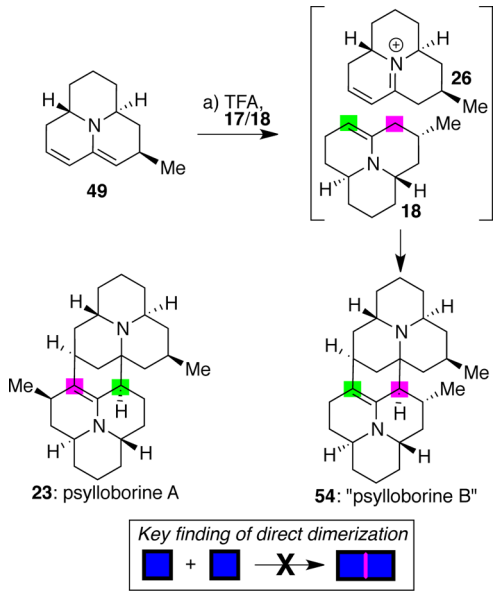
[a]Reagents and conditions: (a) $(COCl)_2$ (1.6 equiv), DMSO (3.2 equiv), Et_3N (6.0 equiv), CH_2Cl_2, −78 to 0 °C, 90 min, 94%; (b) TFA/CH_2Cl_2 (1/1), 0 °C, 1 h, carried forward crude; (c) $RuO_2 \cdot xH_2O$ (0.10 equiv), $NaIO_4$ (4.0 equiv), acetone/H_2O (1:1), 0 °C, 90 min, 77%; (d) *p*-nitrophenol (1.2 equiv), DCC (1.2 equiv), 4-DMAP (0.10 equiv), 25 °C, 20 h; filter, solvent removal, TFA/CH_2Cl_2 (1:1), 0 °C, 1 h; (e) *i*-PrOH (cat.), CH_2Cl_2, 40 °C, 18 h, 31% over two steps; (f) DIBAL-H (2.5 equiv), THF/1,4-dioxane (4:1), 25 °C, 4 min.

readily prepared from **31** in just two steps via oxidation and a one-pot TFA-promoted deprotection/condensation/Mannich reaction sequence. Unfortunately, no conditions were found that could reliably afford **49** from this intermediate. As such, an alternate, slightly longer four-step pathway was developed as shown in the lower half of Scheme 6.[34] The key operation was the final step involving DIBAL-H-mediated reduction of vinylogous amide **53**. This step proceeded in ∼45% conversion (based on crude ^{1}H NMR of samples accounting for full mass recovery) to afford **49** along with the [1,4]-reduced counterpart of **53**. As this critical compound proved unstable and difficult to purify, it was carried forward directly into dimerization studies once formed.

Following extensive experimentation with acid source and solvent, we found that electrophile **26** (Scheme 7) could be obtained when **49** was taken up in CD_2Cl_2 (to enable close monitoring by NMR analysis) and exposed to TFA at 25 °C. When propyleine and isopropyleine (**17** and **18**) were then added as a CD_2Cl_2 solution to this electrophile 2 min later, a new dimeric material was formed over the course of 2 h in 21% overall yield from **53**. Unfortunately, this material did not match the spectral data for either **23** or **24**.[17,18] Extensive NMR analysis (^{1}H, ^{13}C, COSY, TOCSY, NOESY, HSQC, and HMBC; see Supporting Information for full details) ultimately revealed that this dimer was non-natural, resulting from incorrect regiocontrol in the union of the two building blocks, as noted by the highlighted carbons within their frameworks. This result meant that isopropyleine (**18**), not propyleine (**17**), served as the nucleophilic partner. We have elected to give this new dimeric material, compound **54**, the name "psylloborine B", should it ever prove to be a natural isolate.

As indicated in Figure 2, extensive molecular modeling employing hand-held model kits has provided a rationale as to why this outcome may have occurred. Critically, we believe it is the result of kinetic control based on the stereoelectronic and conformational demands of the lone desymmetrizing methyl group within nucleophiles **17** and **18**, not the ratio of these two components in solution. In theory, there are a total of four possible reactive pathways: either propyleine or isopropyleine serving as a nucleophile (with the nucleophilic carbons colored to match that of Scheme 7), with approach of the electrophile

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



[a]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.

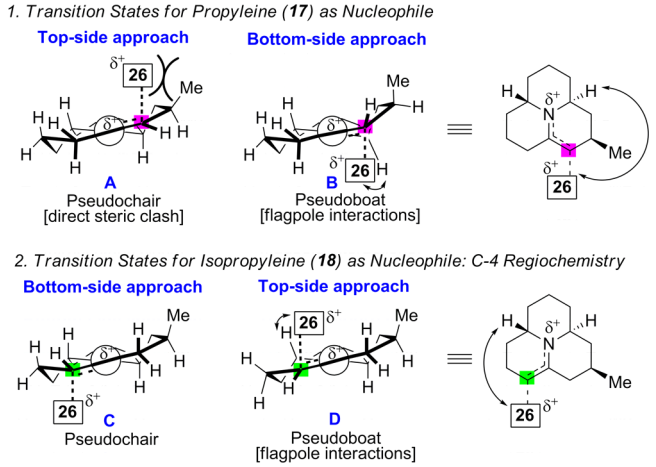


Figure 2. Possible basis for the observed dimerization result based on transition-state models for electrophile addition (i.e., **26**) using either the propyleine (**17**) or isopropyleine (**18**) enamines as nucleophile.

occurring from either the top or bottom face. These possibilities are drawn in Figure 2 as transition states **A**–**D**, all viewed from the perspective of looking down the C–N bond of the enamine, with the nitrogen atom located behind the circle of the Newman projection.

Based on the analysis provided earlier in the context of Scheme 2, the requisite pathway to psylloborine A (**23**) or isopsylloborine A (**24**) would require nucleophilic attack by propyleine (transition states **A** and/or **B**). In transition state **A**, a favorable pseudochair-like transition state can be achieved, but it incurs a significant steric penalty by requiring the incoming electrophile to approach *syn* to the pendant methyl group. In transition state **B**, addition from the bottom face is now *anti* to the pendant methyl group, but it seems to require a pseudoboat-like orientation to proceed, with a number of

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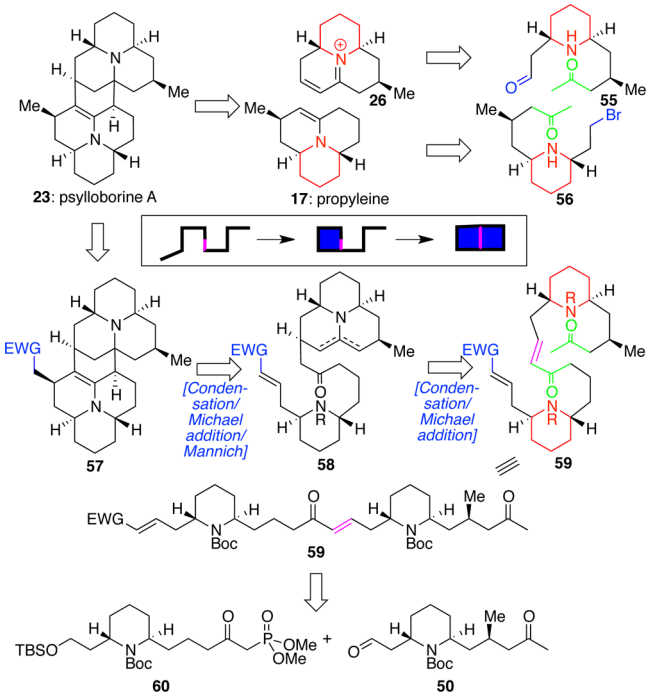
destabilizing flagpole and eclipsing interactions resulting as indicated. By contrast, when isopropyleine (**18**) is the enamine nucleophile (transition states **C** and **D**), there are no proximal substituents that can destabilize the approach of the electrophile as in pathway **A** or **B**. Therefore, the lowest energy pathway is likely to proceed through these transition states, and thus **54** results.[35]

5. Development and Execution of an Alternate Dimerization Strategy. Given this experimental outcome, a new synthetic approach was needed for psylloborine A (**23**) and/or isopsylloborine A (**24**). Ultimately, it was careful consideration of this, as well as other cases where direct dimerization had also failed,[36] which led to the revised retrosynthesis as drawn in Scheme 8. This analysis is based 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 linking can potentially overcome those factors governing intermolecular reactivity.[37] Specifically, rather than combine advanced materials in a final step or merge simpler materials earlier and then elaborate in tandem,[38] 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.

Scheme 8. "Intramolecular Dimerization": An Approach to Consider Deploying When Direct Monomer Coupling Fails to Provide Necessary Unions and/or Stereocenters



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,[39] 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*-Pr_2NEt in CH_3CN at 25 °C) coupled it with aldehyde **50** to afford **65**, with the previously inaccessible intermolecular 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

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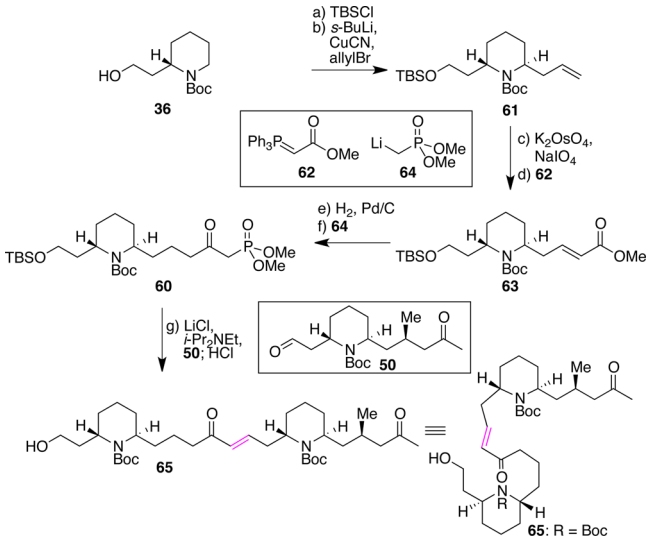
Scheme 9. Synthesis of Key Linking Bond as a Prelude to Testing the Designed Closure Cascades for Psylloborine A and Isopsylloborine A Synthesis[a]



[a]Reagents and conditions: (a) TBSCl (1.1 equiv), imidazole (2.0 equiv), CH_2Cl_2, 25 °C, 19 h; (b) *sec*-BuLi (1.5 equiv), TMEDA (1.6 equiv), Et_2O, −78 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) $K_2OsO_4·2H_2O$ (0.005 equiv), $NaIO_4$ (4.0 equiv), 2,6-lutidine (2.0 equiv), 1,4-dioxane/H_2O (3/1), 25 °C, 2.5 h; (d) **62** (1.22 equiv), CH_2Cl_2, 25 °C, 14 h, 84% over two steps; (e) Pd/C (10%, 0.06 equiv), H_2, MeOH/EtOAc (3/1), −78 to 25 °C, 20 h, 97%; (f) **64** (2.0 equiv), THF, −78 to −45 °C, 1.5 h, 87%; (g) LiCl (4.0 equiv), *i*-Pr_2NEt (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%.

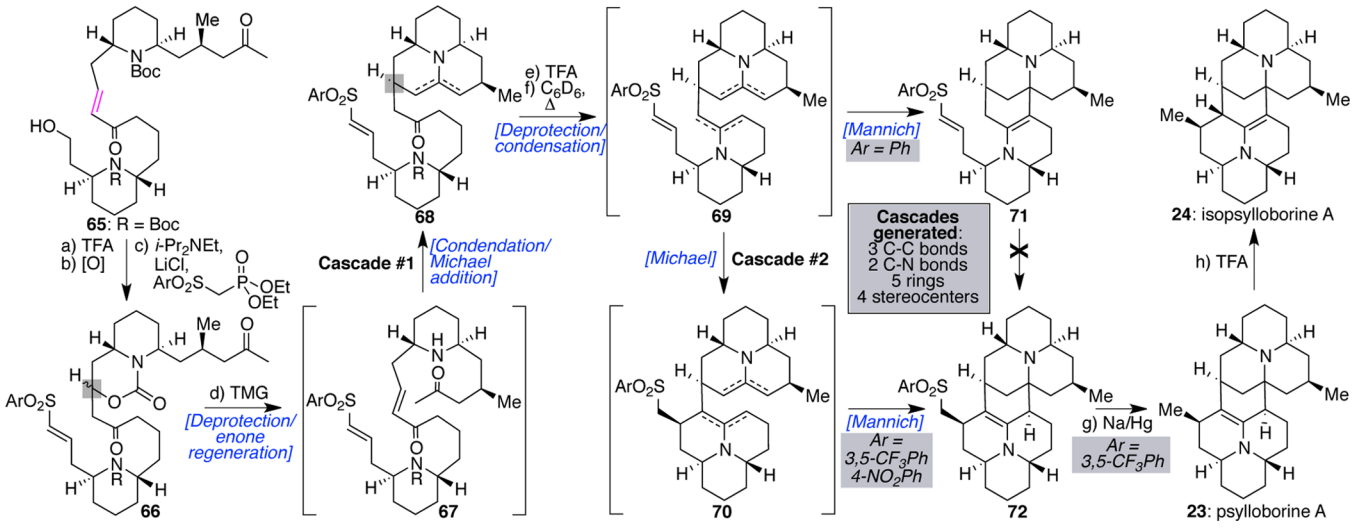
within **66**, that outcome was of no consequence, as this chiral center would be subsequently destroyed. The synthesis of the key precursor (in protected form as **66**) was then completed by oxidizing the alcohol and performing a Horner−Wadsworth−Emmons coupling with an aryl sulfone-containing phosphonate [either Ph-, 3,5-$(CF_3)_2$Ph-, or 4-NO_2Ph-, *vide infra*].[40]

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-tetramethylguanidine (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 CH_2Cl_2 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-d_6 (to monitor the reaction) and heating at 65 °C then initiated that cascade sequence: condensation to **69**, Michael closure to **70**, and a terminating Mannich reaction to complete the synthesis of **72**. As long as the aryl sulfone was sufficiently electron-deficient [i.e., Ar = 3,5-$(CF_3)_2$Ph- or 4-NO_2Ph-], these operations proceeded in the order designed. However, when the unsubstituted phenyl sulfone was used, a large portion of the material appeared to undergo Mannich reaction prior to Michael addition to afford materials believed to have structure **71**.[41] Despite various attempts, these compounds could not be converted into **72**. Thus, the more electron-withdrawing aryl sulfones seem to have enabled the sequence to succeed by ensuring that Michael reaction preceded Mannich closure.

Taken together, these two cascade events arguably constitute the most complex use of condensation/Michael/Mannich

Scheme 10. Total Synthesis of Psylloborine A (23) and Isopsylloborine A (24) via the "Intramolecular Dimerization" Strategy[a]



[a]Reagents and conditions: (a) 10% v/v TFA in CH_2Cl_2 (10 equiv), CH_2Cl_2, −78 °C, 2 h, 89%, 2:1 dr; (b) oxalyl chloride (1.6 equiv), DMSO (3.2 equiv), Et_3N (6.0 equiv), −78 °C, 30 min; 0 °C, 1 h; (c) phosphonate (Ar = 3,5-$(CF_3)_2C_6H_3$, 1.0 equiv), LiCl (2.0 equiv), *i*-Pr_2NEt (2.0 equiv), CH_3CN, 25 °C, 30 min; substrate (1.0 equiv), CH_3CN, 25 °C, 2 h, 67% over two steps (all ensuing yields are for when Ar = 3,5-$(CF_3)_2C_6H_3$); (d) TMG (1.0 equiv), toluene/*i*-PrOH (9:1), 25 °C, 5.5 h, 1:1.2 dr; (e) TFA/CH_2Cl_2, 0 °C, 1 h; (f) C_6D_6, 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), $ClCH_2CH_2Cl$, 75 °C, 30 min, ∼75%.

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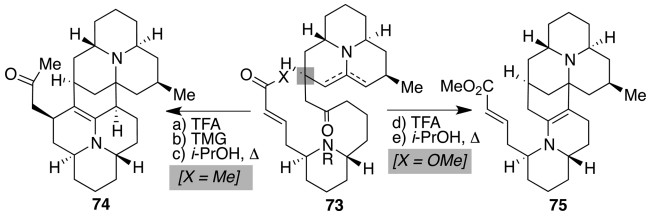
chemistry yet described, given that they involve a total of seven distinct chemical events that forged three C−C bonds, two C−N bonds, five rings, and four stereocenters; the overall yield obtained for the 3,5-$(CF_3)_2$Ph variant, at 15%, reflects a throughput of 79% per chemical transformation. Finally, exposure of the 3,5-$(CF_3)_2$Ph derivative of **72** to Na/Hg amalgam[42] 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 $ClCH_2CH_2Cl$ 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-$(CF_3)_2PhSO_2$- group afforded complete success for the entire sequence, EWGs other than sulfones were also probed for the final cascades. As shown in Scheme 11, use of the same

Scheme 11. Additional Late-Stage Ring Closures: Subtleties in EWG Choice for the Michael System[a]



[a]Reagents and conditions: (a) TFA/CH_2Cl_2, 0 °C, 1 h; (b) TMG (2.0 equiv), *i*-PrOH, 25 °C, 1 h; (c) *i*-PrOH, 60 °C, 2.5 h, 38% yield over three steps; (d) TFA/CH_2Cl_2, 0 °C, 1 h; (e) *i*-PrOH, 80 °C, 2 h, 56% yield over two steps.

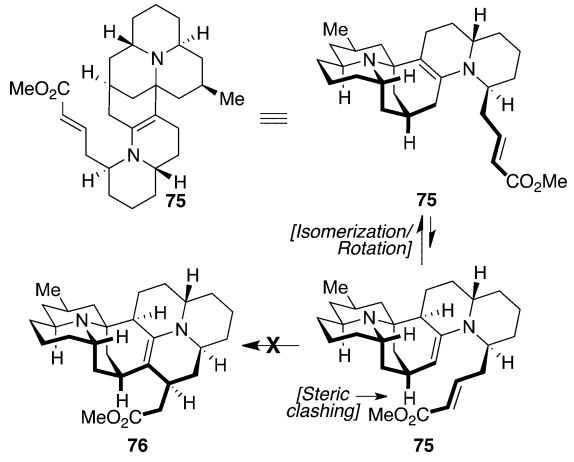
sequence with a simple methyl ketone (i.e., **73**, X = Me) proceeded in similar overall yield (79% per transformation for the steps shown; see Supporting Information) to generate the full heptacyclic core of the dimeric coccinellid alkaloids (**74**). However, no approach could be discovered to convert the methyl ketone to the final pendant methyl of the target natural products. By contrast, use of a simple methyl ester (i.e., **73**, X = OMe), a far easier group to potentially remove, arrested at compound **75** with Mannich closure preceding Michael addition in the second cascade, just as a simple vinyl phenyl sulfone had putatively done (**69** → **71**, Ar = Ph).

Scheme 12 provides a possible graphical explanation for sequence arrest, with steric clashing likely being the basis 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

Scheme 12. Possible Rationale for Cascade Arrest Following Formation of 75



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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(28) When we attempted to forge **31** through methyl addition onto the corresponding enone using $LiMe_2Cu$ in THF at −78 °C, we obtained a 1:3 dr favoring the undesired methyl epimer. It was this result that led us to investigate whether Yamamoto's catalyst and hydride delivery might solve this stereoselectivity challenge. For a review on the stereoselective addition of nucleophiles to enones, see: Howell, G. P. *Org. Process Res. Dev.* **2012**, *16*, 1258.
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(31) These isomers could be chromatographically separated, with re-exposure of the undesired epimer to base affording a 1:1.11 mixture of the two diastereomeric ketones. Intriguingly, use of a similar process by Mueller for desmethyl **48** (ref 15g) afforded a much better ratio of isomers, on the order of 9:1 in favor of the stereogeometry of the highlighted center of **48**. The hypothesized driving force for the epimerization in that case was the ability to minimize the number of C−C and C═O eclipsing interactions; in our case, there are no discernible elements within the two possible structures that appear to influence their relative stabilities, hence why a nearly equimolar mixture forms under thermodynamic conditions.
(32) When ketone **47** was hydrolyzed under mild conditions (25 °C), only material of the configuration of precoccinelline about the highlighted center was obtained; higher temperature and extended reaction times were required to observe any **48**.
(33) Mueller's route to ketone **48** was nine steps and racemic (ref 15g); our route is ten steps but asymmetric.
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(35) We believe that transition state **C** predominates with pseudoaxial attack from the bottom face at C-4 in **18** based on the noted flagpole and eclipsing interactions within **D**; we cannot say for certain, however, whether this component of the analysis is correct, in that the chiral center which would reveal that initial facial preference has been destroyed in the final dimer (i.e., **54**, "psylloborine B").

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(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.
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(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.
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(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.

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