

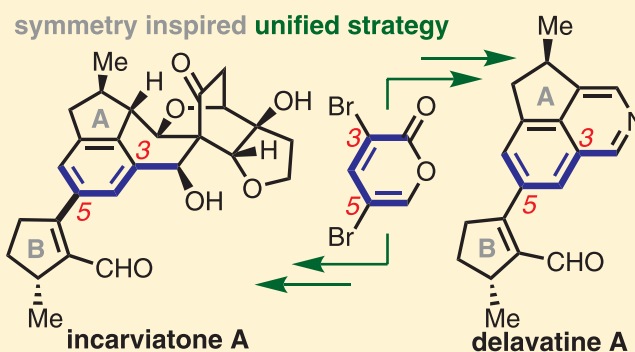
# A Unified Strategy for the Enantiospecific Total Synthesis of Delavatine A and Formal Synthesis of Incarviate A

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**S** Supporting Information

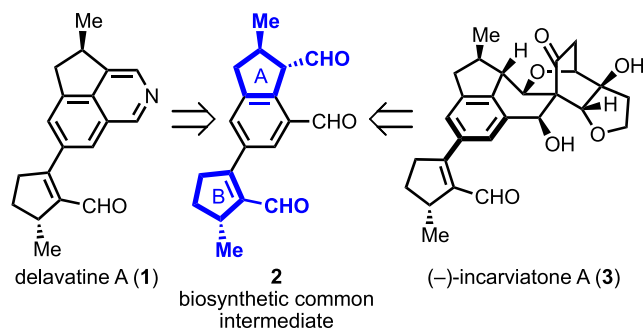
**ABSTRACT:** We describe a symmetry-inspired synthetic approach that has enabled a short synthesis of delavatine A and a formal synthesis of incarviate A, which are two likely biosynthetically related natural products. The indane core of these natural products was constructed through a cascade sequence involving five transformations that occur in a single pot. Leveraging symmetry has allowed us to trace both natural products back to a versatile building block, 3,5-dibromo-2-pyrone, and studies related to site-selective cross-coupling of this polyhalogenated heterocycle are described. In addition, our strategy gave access to a putative biogenetic precursor, from which the syntheses of both natural products were attempted.



## INTRODUCTION

Secondary metabolites (i.e., natural products) serve as an important basis for traditional medicines and pharmaceuticals.<sup>1</sup> Plants of the *Incarvillea* genus, found in the Himalayas and Southwest China, have long been used in traditional Chinese herbal medicine.<sup>2,3</sup> Among the active ingredients responsible for the biological properties of these herbal remedies are alkaloids and a variety of natural product “hybrids”. The latter result from the combination of two or more natural products, or fragments thereof, to furnish structurally interesting compounds with diverse biological properties.<sup>4</sup> *Incarvillea delavayi*, specifically, has been used to treat anemia and dizziness.<sup>5</sup> Two structurally related natural products, delavatine A (**1**, Scheme 1) and incarviate A (**3**), were recently isolated from this flowering plant, each displaying distinct bioactivities and also possessing an unusual molecular scaffold.<sup>6,7</sup>

**Scheme 1. Plausible Common Biosynthetic Precursor of Delavatine A and Incarviate A**



Delavatine A (**1**), a structurally unique alkaloid featuring a cyclopenta[*de*]isoquinoline skeleton, displays micromolar antitumor activity against a variety of human cancer cell lines.<sup>6</sup> On the other hand, incarviate A (**3**) possesses a unique polycyclic skeleton with eight contiguous stereocenters. Initial bioactivity studies have revealed incarviate A to be a monoamine oxidase A (MAO-A) inhibitor.<sup>8</sup> However, comprehensive biological studies of **3** were not conducted due to its poor isolation yield (4.1 mg isolated from 17 kg of dried whole plant).<sup>7</sup> MAO-A antagonists have been implicated in the regulation of cognitive processes such as emotions and certain types of memory<sup>9</sup> as well as in the prevention of tumor proliferation.<sup>10</sup> As such, use of MAO-A inhibitors in the treatment of cancer is currently a hotly pursued research area.<sup>11</sup> Synthesis of unique MAO-A inhibitors like **3** could set the stage for in-depth studies into the connections between MAO-A inhibition and cancer progression.

The low abundance of incarviate A (**3**), together with the intriguing biological activities of **1** and **3**, makes these compounds attractive targets for total synthesis. A total synthesis of **3** was reported by Lei and co-workers in 2015.<sup>12</sup> The first total synthesis of delavatine A (**1**) was then accomplished by Li and co-workers in 2017.<sup>13</sup> While these syntheses each provided access to one of these molecules, we envisioned, instead, a unified approach to both natural products. Recently, we disclosed a modular, four-step synthesis of delavatine A from 3,5-dibromo-2-pyrone.<sup>14</sup> While our previous work reported a short synthesis of delavatine A, in

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this article we describe the evolution of a unified strategy to access both **1** and **3**.

Proposals for the biosynthesis of **1** and **3** have separately invoked trialdehyde **2** as a common intermediate (Scheme 1).<sup>6,7</sup> Synthetic routes that mimic how natural products are formed in plants, often starting from simple building blocks and using highly selective reactions, have long served as a powerful model for designing bioinspired syntheses.<sup>15</sup> In our case, taking inspiration from the putative biosynthetic link between **1** and **2**, we anticipated that a divergent approach involving synthesis and a potentially biomimetic modification of **2** could provide access to both natural products. The success of such a synthetic route would additionally lend credence to the proposed biosyntheses. In the past, this mutually beneficial relationship between biosynthetic hypotheses and organic synthesis has translated into many remarkable total syntheses of natural products in the past several decades.<sup>16</sup>

## RESULTS AND DISCUSSION

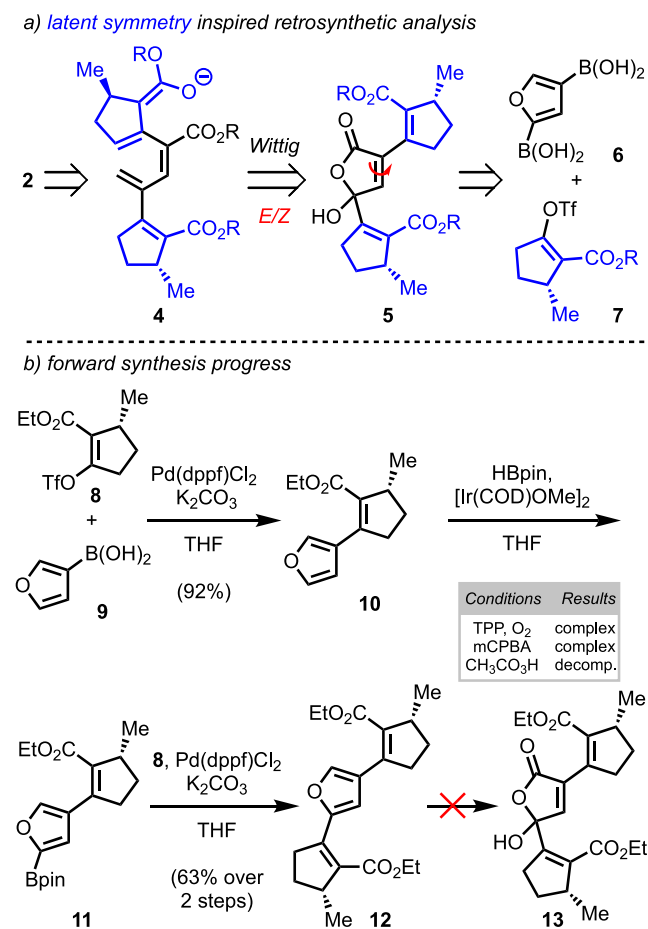
**First Generation Approach.** In determining how to construct **2**, we recognized that this trialdehyde features an element of symmetry (A and B rings, Scheme 1), which we believed could translate into powerful retrosynthetic disconnections. Leveraging symmetry (hidden or overt) is a powerful tool for the identification of simplified precursors, which generally enhances overall synthetic efficiency.<sup>17</sup> From a retrosynthetic perspective, we initially envisioned that **2** could be derived from extended enolate **4**, which would undergo  $6\pi$  electrocyclicization and subsequent reduction of the ester groups in the forward sense (Scheme 2a). In turn, dienolate **4** could be accessed from hydroxybutenolide **5** via Wittig olefination and *E/Z* isomerization. On the basis of the pseudosymmetry of **5**, we traced it back to an envisioned diboronic acid (**6**) and vinyl triflate **7**.

In preliminary synthetic studies, we encountered difficulties in accessing the proposed furan diboronic acid **6**, which was only isolated in trace quantities. We therefore instead turned to a Suzuki coupling between 3-furanylboronic acid (**9**) and known vinyl triflate<sup>18</sup> **8** to furnish monocoupled furan **10** in 92% yield (Scheme 2b). By use of the protocol developed by Hartwig and co-workers,<sup>19</sup> C–H borylation of **10** proceeded efficiently to furnish boronate ester **11**. A second Suzuki coupling between **11** and vinyl triflate **8** then delivered bis-coupled furan **12**. Several oxidation conditions using singlet oxygen or peroxy acids (see Scheme 2b) were explored to convert **12** to butenolide **13**. Unfortunately, all oxidation attempts failed, presumably due to the enhanced  $\pi$ -deficiency of furan **12**, now bearing two electron-withdrawing groups.

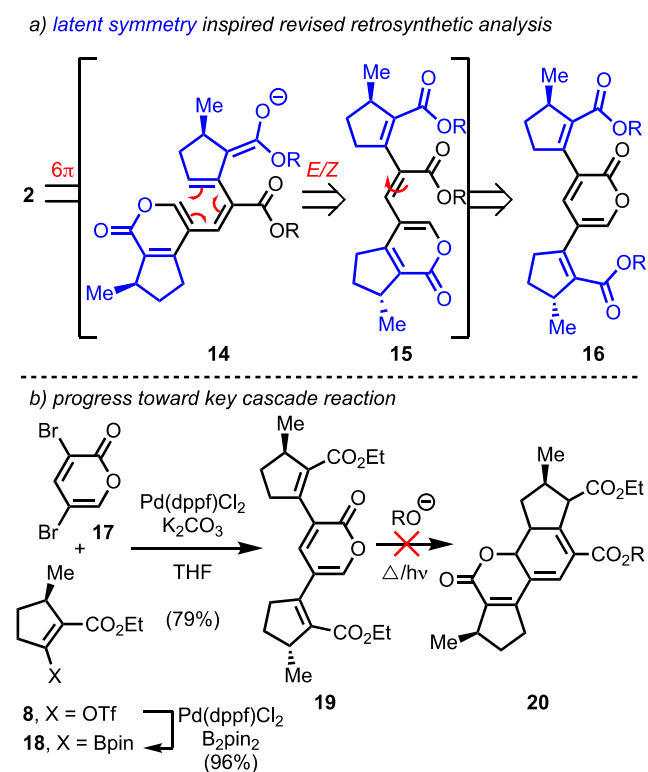
**Second Generation Approach.** In light of our inability to oxidize furan **12** to the corresponding hydroxybutenolide, we designed an alternative retrosynthesis. Our revised strategy called for the construction of the indane core of **2** via the intermediacy of dienolate **14** (cf. **4**, Scheme 2a), which in turn would arise from highly conjugated polyene **15** upon isomerization. We anticipated that an equilibrium could be established between polyene **15** and bis-coupled pyrone **16** in the presence of an alkoxide nucleophile. We anticipated that this entire transformation (**16**  $\rightarrow$  **14**, Scheme 3a) might be performed as a one-pot cascade, which would be initiated through transactonization of bis-coupled pyrone **16** with an alkoxide.

On the basis of this revised retrosynthetic plan and as the first step toward preparation of bis-coupled pyrone **16**, a

## Scheme 2. Symmetry-Inspired First Generation Approach



## Scheme 3. Revised Retrosynthetic Analysis and Preliminary Attempts To Initiate the Cascade Sequence



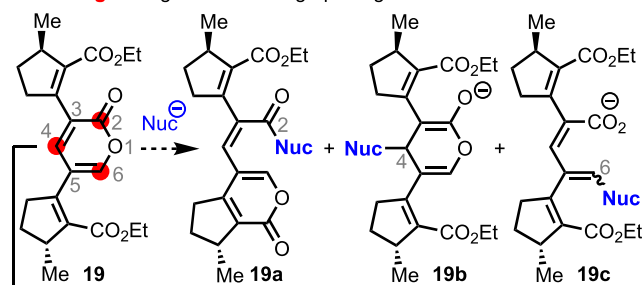
Suzuki–Miyaura borylation of vinyl triflate **8** furnished boronate ester **18** in 96% yield (Scheme 3b). Subsequent Suzuki cross-coupling between 3,5-dibromo-2-pyrone<sup>20</sup> (**17**) and **18** provided bis-coupled pyrone **19** in 79% yield. With **19** in hand, we were in a position to experimentally assess methods to initiate the envisioned cascade sequence (i.e., **16** → **14**, Scheme 3a). Initial efforts focused on treating **19** with nucleophilic alkoxides under different conditions. Opening 2-pyrones with an alkoxide in a 1,2-fashion,<sup>21</sup> as would be ideal for our synthetic plan, has precedent in related systems. However, under both thermal and photolytic conditions, we were unable to isolate any promising intermediates toward the envisioned cascade product (i.e., **20**).

Given the lack of initial success with alkoxide-initiated openings, we began to investigate other nucleophiles known to react with 2-pyrones.<sup>22</sup> Notably, pyrone **19** features electrophilic sites at C2, C4, and C6 (Scheme 4a), and consequently,

#### Scheme 4. Nucleophilic Ring-Opening of Bis-Coupled Pyrone **19** with Cyclic Amines

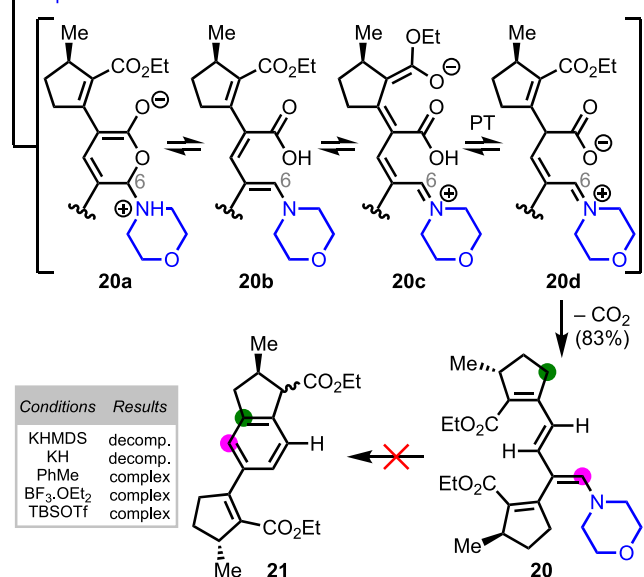
(a) possible reactive sites in bis-coupled pyrone **19**

challenges: regioselective ring opening



(b) 1,6-ring opening of bis-coupled pyrone **19** with cyclic amine

morpholine



three different constitutional isomers can be expected upon treatment with nucleophiles under varying reaction conditions. The relative reactivity of each of the electrophilic sites on 2-pyrones varies significantly depending on the nature of substituents.<sup>21c</sup> In bis-coupled pyrone **19**, which is substituted with the same electron-withdrawing moieties at C3 and C5, it was challenging to predict the preferred reactive site of the

nucleophilic attack. Among the three constitutional isomers, the product resulting from nucleophilic C4-ring-opening (**19b**) would be the least beneficial for our synthesis, whereas we believed that accessing either C2-ring opened product **19a** or C6-ring opened product **19c** would be productive for our synthesis.

With these possibilities for nucleophilic opening in mind, bis-coupled pyrone **19** was treated with a variety of nucleophiles (see the Supporting Information for all the attempted nucleophiles).<sup>23</sup> Among the nucleophiles that were investigated, we observed our first successful ring-opening upon treating **19** with cyclic amines.<sup>24</sup> As outlined in Scheme 4b, morpholine opened **19** in a 1,6-fashion to furnish the decarboxylated enamine **20**, which was isolated in 83% yield as a single diastereomer. The connectivity in **20** was validated by 2D NMR analysis, and the reaction was found to work equally well with other cyclic amines, such as piperidine and pyrrolidine. Although cyclic amines proved fruitful in opening **19**, we were unable to avoid the spontaneous decarboxylation event, even by adding an alkylating agent aimed at intercepting the intermediate carboxylate.

We postulate that morpholine (like the other cyclic amines) reacts with **19** to give adduct **20a**, which opens in a 1,6-fashion to provide enamine **20b**. The latter compound might then undergo proton transfer to furnish carboxylate ion **20d** presumably via iminium ion **20c**. The carboxylate group, now connected to a sp<sup>3</sup>-hybridized carbon in **20d**, would undergo rapid decarboxylation to furnish **20**. Because the carboxylate group was essential to access either of the targeted natural products, this route was ultimately unworkable. However, cognizant that the lost carboxylate group could be reinstalled at a later stage via a transition metal-catalyzed C–H activation reaction,<sup>25</sup> we continued to explore the benzannulation with enamine **20**. We thus attempted to forge the indane core of **21** through an isomerization/6 $\pi$  electrocyclicization/elimination cascade sequence starting from enamine **20**. Mechanistically, the ring closure can also be considered a 6-*endo*-trig Michael-type addition of the generated enolate. Disappointingly, all the acidic and basic reaction conditions (see Scheme 4b for selected conditions) that were investigated returned inseparable product mixtures or led to nonspecific decomposition of **20**.

Given our failure to convert enamine **20** to the indane core in **21**, we began investigating alternative nucleophiles for opening bis-coupled pyrone **19** to access a suitable adduct for the subsequent isomerization/6 $\pi$  electrocyclicization/elimination cascade. Pyrone **19** was subjected to several nucleophiles (sodium azide, hydrides, imides, thiols, enolates, Grignard reagents, sodium thiocyanate, and sodium cyanide) under a variety of reaction conditions. To our delight, of these, sequential treatment of **19** with sodium cyanide and methyl iodide, inspired by the precedent of work conducted by Vogel,<sup>26</sup> delivered methyl ester **22** as an inseparable 4.5:1 mixture of diastereomers (Scheme 5).

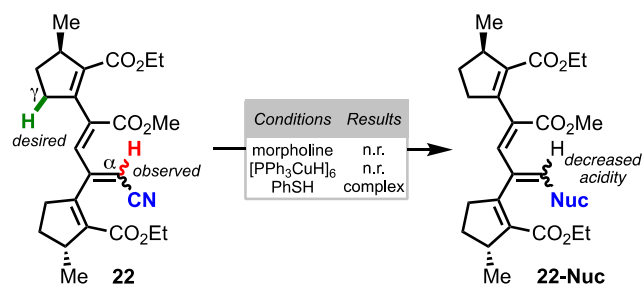
Likely, the cyanide anion undergoes 1,6-addition to provide nitrile **22a**, which then opens to generate carboxylate ion **22b**. The carboxylate group, now appended to a sp<sup>2</sup>-hybridized carbon, unlike in intermediate **20d** (Scheme 4b), does not suffer spontaneous decarboxylation and can be trapped with an alkylating agent to furnish methyl ester **22**. Having gained access to methyl ester **22**, we then investigated various conditions to form the requisite enolate that would induce the 6 $\pi$  electrocyclicization/6-*endo*-trig Michael-type addition to



alkene group either was thermodynamically driven or resulted from deprotonation–protonation of the vinyl hydrogen under the basic reaction conditions. Having now locked the configuration and conformation of the triene by installation of the imide, we investigated the desired ring closure by treating imide **29** under a variety of enolization conditions. Unfortunately, all the conditions that were surveyed led to nonspecific decomposition or returned unreacted **29**.

At this stage, we were confident that the deprotonation of the vinyl hydrogen rather than the desired  $\gamma$ -deprotonation of the  $\alpha,\beta$ -unsaturated ester moiety constituted a key problem (Scheme 7). To circumvent this issue, we envisioned pursuing

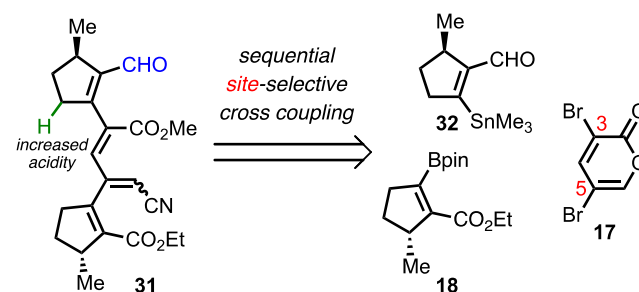
#### Scheme 7. Nucleophilic Substitution of Nitrile Group in Methyl Ester **22**



two modified approaches: (a) we could either attempt to open bis-coupled pyrone **19** or substitute the nitrile group in **22** or **23** with a nucleophile that would render the vinyl hydrogen less acidic; or alternatively (b) we could synthesize a derivative similar to **22** that contains a more electron-withdrawing substituent in the northern cyclopentenyl ring which would enhance the acidity of the  $\gamma$ -hydrogen. Given our inability to open bis-coupled pyrone **19** with nucleophiles other than cyclic amines (Scheme 4b) and cyanide ion (Scheme 5), we instead chose to attempt a nucleophilic vinylic substitution of the nitrile group in either **22** or **23**. Toward this end, **22** was treated with a variety of nucleophiles (see Scheme 7 for selected conditions) to substitute the nitrile group via 1,6-addition–elimination to generate methyl ester **22-Nuc**. To our dismay, all the nucleophiles that were investigated either returned unreacted methyl ester **22** or resulted in complex product mixtures. A similar outcome was encountered when isomerized methyl ester **23** was treated with a variety of nucleophiles.

Because of the difficulties associated with decreasing the acidity of the vinyl hydrogen, we at this stage decided to proceed with the alternative approach (b), in which a derivative of **22** bearing a relatively more electron-withdrawing functional group on the northern ring needed to be synthesized. As outlined in Scheme 8, we sought to prepare aldehyde **31**, which features a more acidic  $\gamma$ -hydrogen compared to **22** and where deprotonation of the  $\gamma$ -hydrogen should be favored over abstraction of the undesired vinyl hydrogen. In our previously described Suzuki coupling to synthesize bis-coupled pyrone **19** from 3,5-dibromo-2-pyrone (**17**) and boronate ester **18**, the order of reactivity at the 3- or 5-position of **17** was inconsequential since equivalent coupling partners were introduced. However, by incorporation of different substituents on the cyclopentenyl moieties in aldehyde **31**, the synthesis of **31** now called for a site-selective cross-coupling of 3,5-dibromo-2-pyrone (**17**). If this type of selective coupling could be achieved, aldehyde **31** could be

#### Scheme 8. Retrosynthetic Analysis Involving Sequential Site-Selective Cross-Coupling of 3,5-Dibromo-2-pyrone



conveniently traced back to 3,5-dibromo-2-pyrone (**17**), boronate ester **18**, and known stannane aldehyde **32**.

**Site-Selective Cross-Coupling Studies.** 3,5-Dibromo-2-pyrone (**17**) belongs to a class of  $\alpha$ -pyrone-derived polyhalogenated heterocycles<sup>28</sup> that possess two chemically inequivalent C–Br bonds.<sup>29</sup> In general, retrosynthetic analyses involving site-selective cross-coupling of polyhalogenated heterocycles enable identification of drastically simplified precursors,<sup>30</sup> and this has been exploited in both academic and industrial settings.<sup>31</sup>

Cho and co-workers have previously reported site-selective modifications of 3,5-dibromo-2-pyrone (**17**) in a variety of cross-coupling processes leading to formation of constitutionally isomeric products.<sup>32–34</sup> In addition, the same group also reported efficient total syntheses of natural products by employing site-selective cross-coupling of 3,5-dibromo-2-pyrone (**17**).<sup>35</sup> While these studies enabled identification of factors important for site-selective cross-coupling with **17**, a comprehensive mechanistic reasoning for the observed selectivity was not established. While several studies have sought to predict and rationalize the selectivity in reactions of polyhalogenated heterocycles, it has generally remained challenging.<sup>29,30a</sup> In some cases, consideration of <sup>1</sup>H NMR chemical shifts of the C–H bonds in the parent non-halogenated heterocycles have guided the prediction of site-selective cross-couplings in the corresponding polyhalogenated heterocycles.<sup>36</sup> However, the predicted outcome by employing this method was contrary to the observed site selectivity in 3,5-dibromo-2-pyrone (**17**).<sup>29</sup> Following this observation, the mechanistic reasoning for the observed site selectivity in **17** has remained largely unexplored.

Taking inspiration from a report by Cho and co-workers,<sup>34</sup> we investigated the Suzuki coupling reaction between 3,5-dibromo-2-pyrone (**17**) and commercially available phenylboronic acids (Table 1). We identified that solvent choice, temperature, and addition of copper(I) iodide (CuI) appeared to have a marked influence on the observed coupling selectivity in **17**. Our studies, together with the seminal results obtained by Cho and co-workers, culminated in the conclusion that in nonpolar solvents such as 1,2-dichloroethane, tetrahydrofuran, and toluene the C3-coupled product **33** was primarily formed. In addition, neither the addition of CuI nor conducting the reaction at elevated temperature influenced the observed C3-coupling in nonpolar solvents. In contrast, when the reaction was conducted in polar solvents such as dimethyl sulfoxide, dimethylformamide, and acetone, the C5-coupled product **34** was generally formed as the major product. Notably, the C5-coupled product **34** was observed only in the presence of CuI.<sup>14</sup> In other words, conducting the reaction in the absence

Table 1. Suzuki Couplings with 3,5-Dibromo-2-pyrone

$\epsilon^a$	Solvent	yield <sup>b</sup> (%) 33:34:35			
		With CuI 23 °C		Without CuI 23 °C	
47	DMSO	nd:12:nd	8:13:nd	nr	— <sup>c</sup>
38.25	DMF	nd:18:nd	15:37:nd	nr	tr:nd:nd
21.01	acetone	tr:32:nd	16:29:nd	nr	53:nd:nd
10.42	DCE	57:13:nd	58:tr:11	nr	70:nd:nd
7.52	THF	27:8:nd	49:17:nd	nr	47:nd:19
2.38	toluene	55:tr:nd	56:tr:tr	nr	52:nd:nd

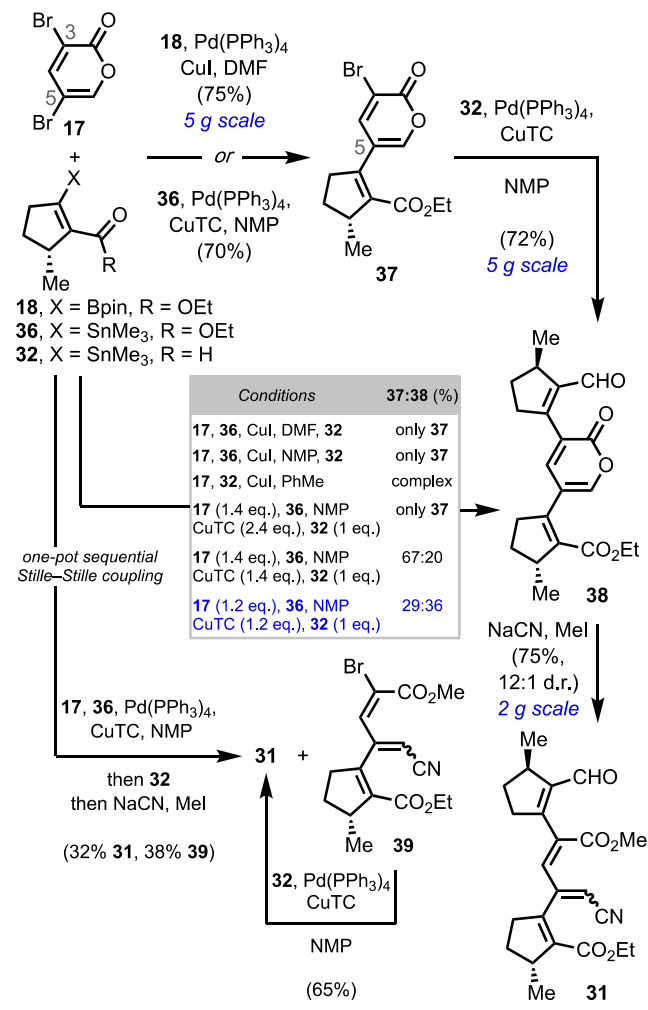
<sup>a</sup>Dielectric constant at 20 °C.<sup>38</sup> <sup>b</sup>Determined by <sup>1</sup>H NMR using 1,1,2,2-tetrachloroethane as an internal standard. <sup>c</sup>Decomposition of 17. Conditions: PhB(OH)<sub>2</sub> (1.2 equiv), Pd(PPh<sub>3</sub>)<sub>4</sub> (10 mol %), CuI (1.0 equiv), K<sub>2</sub>CO<sub>3</sub> (2.0 equiv), solvent (0.1 M). nd = not detectable, tr = trace, and nr = no reaction.

of CuI exclusively generated the C3-coupled product 33.<sup>37</sup> Unlike the results reported by Cho and co-workers, we did not observe a switch in C3/C5 selectivity as the temperature was raised from 23 to 50 °C.<sup>34</sup>

We thus identified the selectivity of cross-coupling with 3,5-dibromo-2-pyrone (17) to be temperature independent and to proceed exclusively at C3 in nonpolar solvents in both the presence and absence of CuI, while coupling is favored at C5 in polar solvents but only in the presence of CuI. Furthermore, we strove to gain mechanistic insight into the observed site selectivity in 17 by computational methods. A detailed account of this collaborative work and the cumulative mechanistic insight was described in our initial publication that focused on delavatine A.<sup>14</sup>

**Forward Synthesis To Access Delavatine A (1).** With the conditions for site-selective cross-coupling of 3,5-dibromo-2-pyrone (17) established, we commenced our forward synthesis to access aldehyde 31 (Scheme 9). We envisioned selectively coupling the C5 position in 17 with boronate ester 18, which following our studies would be achieved by use of both a polar solvent and addition of CuI. Indeed, the Suzuki coupling between 17 and 18 in dimethylformamide in the presence of CuI proved successful and gave monocoupled pyrone 37 in 75% yield on a multigram scale. Analogously, a site-selective Stille coupling between 17 and stannane ester 36 also furnished 37 in 70% yield, when conducted in *N*-methyl-2-pyrrolidone (NMP) in the presence of copper(I) thiophene-2-carboxylate (CuTC). A subsequent Stille coupling between monocoupled pyrone 37 and stannane aldehyde<sup>13a</sup> 32 then delivered bis-coupled pyrone 38 in 72% yield on a multigram scale. A significant side reaction in this Stille coupling was the formation of the corresponding homocoupled product of stannane aldehyde 32. Fortunately, this undesired side reaction could be eventually suppressed by using 32 as a limiting reagent. Subjecting monocoupled pyrone 37 to the previously established ring-opening conditions with cyanide ion gave rise to aldehyde 31 in 75% on a multigram scale.

Scheme 9. Forward Synthesis To Access Aldehyde 31



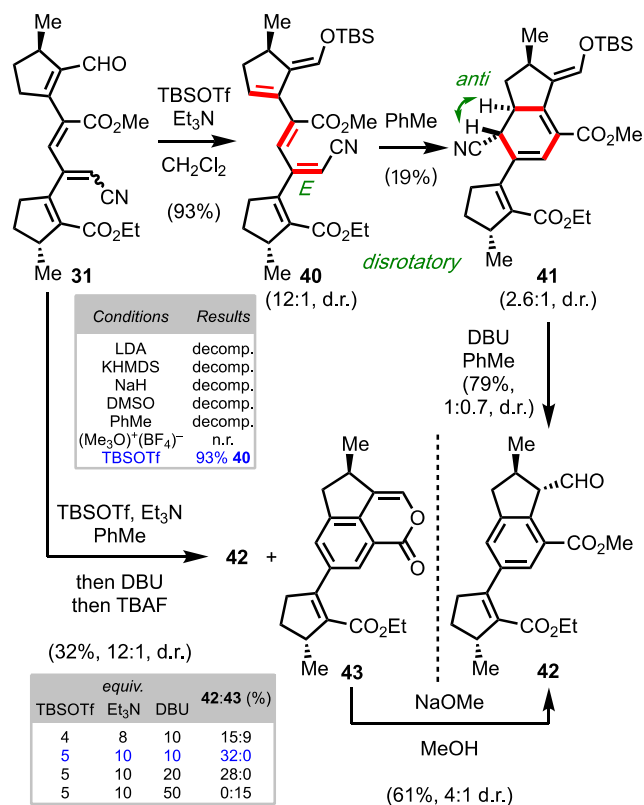
Because of the similarity in reaction conditions of the first Suzuki/Stille coupling to generate monocoupled pyrone 37 and the second Stille coupling to furnish bis-coupled pyrone 38, we began exploring conditions to accomplish a sequential Suzuki/Stille–Stille coupling to directly access 37 from 3,5-dibromo-2-pyrone (17) in a single pot. We initially studied the sequential Suzuki–Stille coupling in a single pot. However, under all the attempted conditions, nonspecific decomposition of stannane aldehyde 32 was observed, and only the monocoupled pyrone 37 was isolated. Similar results were observed when sequential Stille–Stille coupling was performed by using CuI as the copper source. Attempts to achieve a site-selective C3-coupling between 17 and 32 prior to the second Stille coupling were also met with failure. Eventually, we realized that the addition of CuTC was crucial for enabling the sequential and one-pot Stille–Stille coupling, and bis-coupled pyrone 38 was obtained in comparable yield. With these established conditions, pyrone opening with cyanide ion was also attempted in the same pot to furnish aldehyde 31 directly from 3,5-dibromo-2-pyrone (17). Excitingly, the one-pot sequential Stille–Stille–pyrone opening sequence, which generates a remarkable amount of target-relevant molecular complexity in a single step, was successful and furnished 31 in 32% overall yield. A significant amount of bromide 39 was obtained as a byproduct in the sequential Stille–Stille–cyanide opening sequence, which results from opening of the residual

monocoupled pyrone **37** (generated in the first Stille coupling). Fortunately, bromide **39** could be subjected to Stille coupling with stannane aldehyde **32** to furnish aldehyde **31**, thus resulting in a net 57% combined yield of **31** starting from 3,5-dibromo-2-pyrone (**17**).

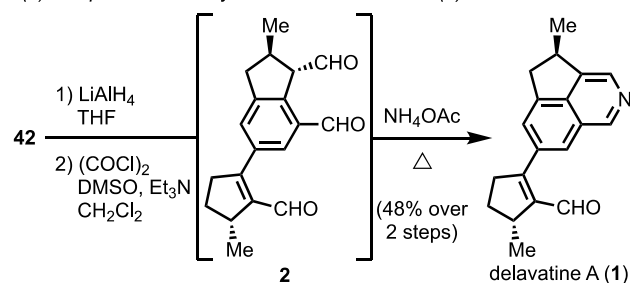
With aldehyde **31** in hand, we next turned our attention to investigating whether the  $\gamma$ -deprotonation of the  $\alpha,\beta$ -unsaturated ester moiety could be achieved over deprotonation of the vinyl hydrogen in **31** (Scheme 10). Toward this end, **31**

### Scheme 10. Completion of the Synthesis of Delavatine A (1)

(a) development of the one-pot cascade sequence



(b) completion of the synthesis of delavatine A (1)



was treated under a variety of basic reaction conditions (selected conditions shown in Scheme 10). We observed rapid decomposition of **31** upon exposure to strong bases such as LDA, LHMDS, or NaH. In addition, a similarly dissatisfying result was observed when **31** was subjected to the previously established *E/Z*-isomerization conditions (cf. **22** → **23**, Scheme 5). Acidic conditions similarly met with failure. Fortunately, when aldehyde **31** was subjected to soft enolization conditions (TBSOTf, Et<sub>3</sub>N), silyl enol ether **40** was isolated as a mixture of diastereomers (12:1) in 93% yield

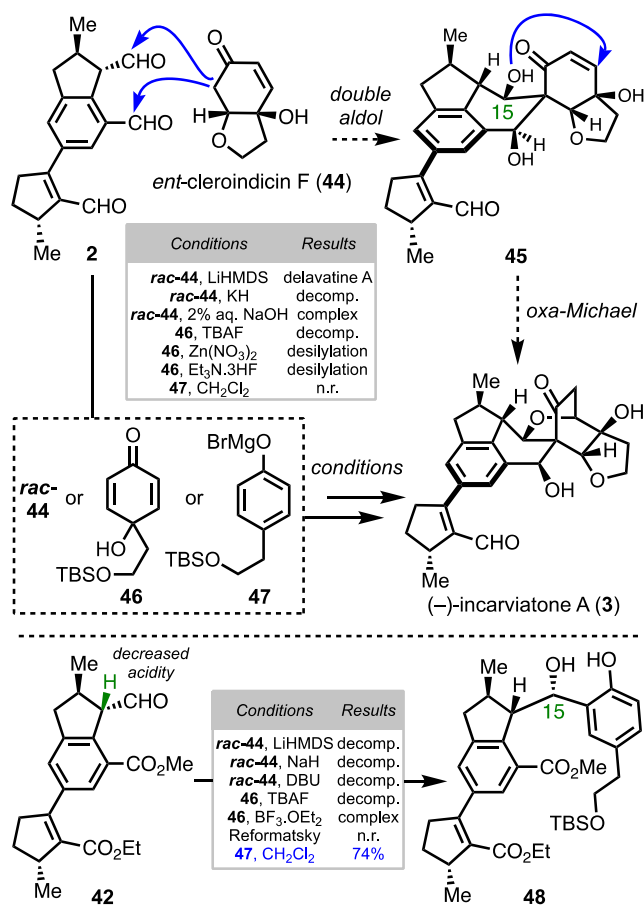
and the vinyl nitrile group remained untouched. Chromatographic separation of the product mixture revealed that the major component was the *E*-isomer. Our initial investigations with silyl enol ether **40** included attempting several Mukaiyama–Michael-type reactions to effect the ring closure via the previously proposed 6-*endo*-trig Michael-type addition pathway. However, all these conditions did not give rise to any of the desired cyclized product. Eventually, it was discovered that the ring closure, proceeding via initial isomerization followed by 6 $\pi$  electrocyclization,<sup>40</sup> simply occurred upon heating **40** in toluene at elevated temperature. The intermediate cyclized product (**41**) was then converted to indane aldehyde **42** (1:0.7 d.r.) upon treatment with diazabicyclo[5.4.0]undec-7-ene (DBU). The 6 $\pi$  electrocyclization gave rise to two diastereomers in a 2.6:1 ratio, where the highlighted hydrogen atoms adopt an *anti*-relationship, as determined by analysis of the coupling constants in the <sup>1</sup>H NMR spectrum. This observation indicates a thermally favored disrotatory ring closure<sup>41</sup> of the major *E* isomer of silyl enol ether **40**.

We then turned toward translating this three-step sequence (**31** → **42**) into a one-pot cascade sequence.<sup>42</sup> Our initial studies aimed at achieving this entire transformation in a single pot involved sequential addition of reagents. Eventually, we realized that the equivalents of *tert*-butyldimethylsilyl-trifluoromethanesulfonate (TBSOTf), triethylamine, and DBU had a profound impact on the isolated yield of indane aldehyde **42** (selected conditions shown in Scheme 10). We observed that a relatively small excess of TBSOTf and trimethylamine gave a mixture of both indane aldehyde **42** and benzocoumarin **43**, while the use of a very large excess of DBU exclusively provided benzocoumarin **43** in poor yield. Following careful optimization, a 10-fold excess of both DBU and trimethylamine was determined to be optimal to exclusively obtain indane aldehyde **42** in 32% yield (12:1 d.r.). It should be noted that hydrolyzing the intermediate silyl enol ether of this three-step sequence with TBAF furnished **42** with a better diastereoselectivity (12:1 d.r.) compared to when **42** was obtained from **41** (1:0.7 d.r.). The observed diastereoselectivity could be a result of the “buffered” TBAF conditions in the one-pot cascade sequence, which we believe could alter the thermodynamic distribution of the corresponding diastereomers. In addition, it was found that benzocoumarin **43** could be converted to indane aldehyde **42** by treatment with sodium methoxide in methanol. It was later found that in addition to the TBS silyl enol ether the corresponding TIPS silyl enol ether also proved to be a suitable precursor for the synthesis of **42** via the established cascade sequence. The indane aldehyde **42** was then reduced with lithium aluminum hydride to the corresponding triol, which when subjected to Swern oxidation furnished the proposed biosynthetic common intermediate, trialdehyde **2**. Finally, **2** was treated *in situ* with ammonium acetate along with moderate heating to provide delavatine A (**1**) in 48% yield over two steps starting from **42**. Delavatine A prepared through the sequence of steps described here possessed analytical data (<sup>1</sup>H and <sup>13</sup>C NMR, HRMS, IR, [ $\alpha$ ]<sub>D</sub>), in full agreement with those reported for the naturally occurring material.<sup>5</sup> Failing to heat the mixture after addition of ammonium acetate resulted in formation of an inseparable mixture of delavatine A along with its isomer featuring a deconjugated enal moiety.<sup>43</sup> Following this synthetic sequence, we were able to access delavatine A (**1**) in only four steps from the known compounds 3,5-dibromo-2-pyrone (**17**), stannane

aldehyde **32**, and stannane ester **36** (or in a longest linear sequence of 10 steps from commercially available (*R*)-pulegone).

**Forward Synthesis To Access Incarviationone A (3).** Our synthesis of delavatine A (**1**) was accomplished from its putative biosynthetic precursor **2**, which had not been reported in any of the previous syntheses of **1** or the structurally related incarviationone A (**3**).<sup>12,13a</sup> We believed access to **2** might also enable a bioinspired synthesis of **3**. As outlined in Scheme 11,

**Scheme 11. Bioinspired Attempts To Synthesize Incarviationone A (3)**



bioynthetically, it has been hypothesized that a double aldol reaction of aldehyde **2** with *ent*-cleroindicin F (**44**), a benzofuranone analogue coisolated with **3**,<sup>7</sup> forms the structurally unique hybrid **45**. Finally, an intramolecular *oxa*-Michael addition of the C15 hydroxy group of **45** into the cyclohexanone moiety would give rise to incarviationone A (**3**).<sup>7</sup> On the basis of this proposal, we planned to use ( $\pm$ )-cleroindicin F (*rac*-**44**) or silyl ether<sup>45</sup> **46** to convert trialdehyde **2** to incarviationone A (**3**) via the proposed biosynthetic pathway. To our surprise, trialdehyde **2** was stable to silica and was isolated in 53% yield over two steps starting from indane aldehyde **42**. ( $\pm$ )-Cleroindicin F (*rac*-**44**) was accessed from tyrosol in a known three-step sequence proceeding via **46**.<sup>45</sup> Strategically and for practical reasons, we investigated the double aldol reaction using racemic ( $\pm$ )-cleroindicin F (*rac*-**44**) rather than the optically pure analogue. While we believed that under the aldol reaction conditions *rac*-**44** would be in equilibrium with its retro-*oxa*-Michael product (i.e., the desilylated derivative of **46**), the adduct of **2** and **44**

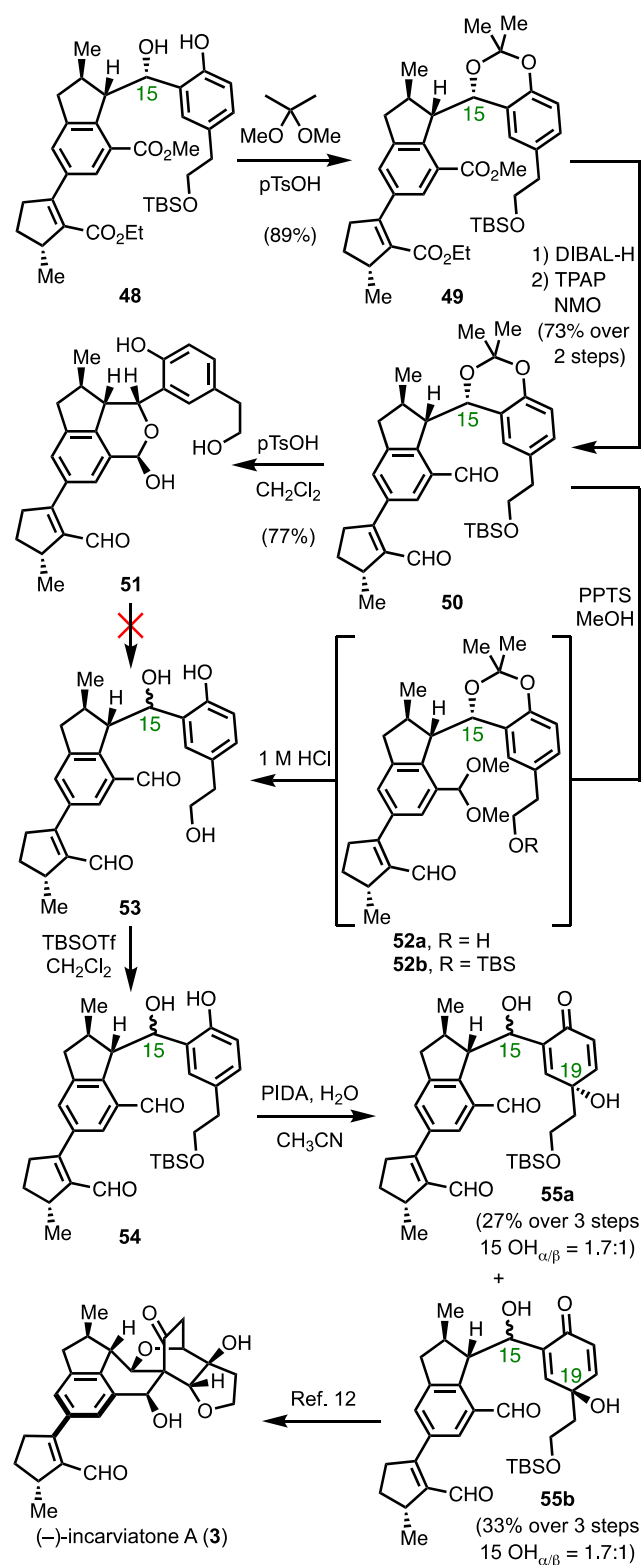
(**45**) could also revert to the corresponding starting materials. Thus, only the final intramolecular *oxa*-Michael addition should drive the equilibrium toward the formation of **3**, while all preceding reactions would be highly reversible. Consequently, we hypothesized that the stereochemistry of the aldol and Michael addition products could be funneled to provide the stereochemical configuration as found in incarviationone A (**3**).<sup>12</sup> Following similar reasoning, we also attempted to initiate the biomimetic cascade sequence with silyl ether **46**, where we believed the corresponding enolate could be generated upon treatment with a fluoride source that would lead to sequential desilylation and *oxa*-Michael addition.

Notable aspects of our attempted conditions (selected conditions shown in Scheme 11) include (a) using HMDS-derived bases primarily resulted in isolation of delavatine A (**1**) due to condensation of trialdehyde **2** with the resulting HMDS, (b) other basic conditions either returned unreacted starting materials or formed complex product mixture, and (c) attempts to generate the enolate derived from silyl ether **46** also led to unsatisfactory results and either the desilylated quinol was isolated or nonspecific decomposition was observed. Inspired by the studies of Lei and co-workers in their synthesis of incarviationone A,<sup>12</sup> we attempted to conduct a phenol aldol reaction between **2** and magnesium phenolate **47**. Unfortunately, this reaction exclusively returned unreacted trialdehyde **2**. At this stage, we hypothesized that our unsatisfactory results might originate due to the presence of the highly acidic  $\alpha$ -hydrogen of the aldehyde group. We reasoned that the basic reaction conditions might lead to the enolate derived from trialdehyde **2**, thus inhibiting nucleophilic addition into the aldehyde group.

To circumvent the putative equilibration to the undesired enolate of **2**, we decided to conduct the aldol reaction with a derivative of trialdehyde **2**, where the acidity of the  $\alpha$ -hydrogen is tempered. Toward this end, we decided to pursue further studies with indane aldehyde **42** bearing two ester groups. Attempts to conduct the aldol reaction between **42** and ( $\pm$ )-cleroindicin F (*rac*-**44**) under a variety of basic conditions (see Scheme 11 for selected conditions) primarily resulted in nonspecific decomposition of **42**. Similar results were observed when silyl ether **46** was employed as the substrate. Mild conditions for the Reformatsky reaction between **42** and several model activated organozinc reagents were also explored. Unfortunately, under all these conditions, we mainly isolated unreacted indane aldehyde **42**. To our delight, when **42** and magnesium phenolate **47** were subjected to phenolate aldol conditions (as described by Lei and co-workers),<sup>12</sup> we exclusively isolated diol **48** as a single diastereomer in 74% yield. It should be noted that the stereochemical configuration at C15, which was assigned by characterizing a later stage intermediate, is opposite to the one observed in incarviationone A (**3**). However, we chose to continue with this intermediate with the aim of inverting the C15 stereochemistry at a later stage.<sup>46</sup>

With diol **48** in hand, we began exploring a variety of options to temporarily protect the diol moiety to effect conversion of the esters to the corresponding aldehyde groups. Toward this end, treatment of diol **48** with 2,2-dimethoxypropane furnished acetonide **49** (Scheme 12). Use of both a cyclic siloxane<sup>47</sup> or a boronic ester<sup>48</sup> as protecting groups proved ineffective as these groups were susceptible to the ensuing reducing conditions. DIBAL-H reduction of **49** followed by Ley-Griffith oxidation<sup>49</sup> gave rise to dialdehyde

Scheme 12. Completion of the Formal Synthesis of Incarviate A (3)



50 in 73% yield over two steps. Selective deprotection of the diol moiety in the presence of the primary silyl ether group was exceedingly challenging, and nonspecific decomposition of dialdehyde 50 was observed under a wide variety of conditions. During the course of our investigations, we observed formation of hemiacetal 51, when 50 was treated with a stoichiometric

amount of *p*-toluenesulfonic acid in dichloromethane as the solvent. Hemiacetal 51 proved to be very stable under both acidic and basic conditions, and extensive characterization of this compound enabled us to establish the stereochemical configuration at C15 in diol 48. Ultimately, treatment of dialdehyde 50 with catalytic pyridinium *p*-toluenesulfonate afforded a mixture of acetals 52a and 52b. The acetals generated *in situ* were then treated with aqueous hydrogen chloride solution to give the desired globally deprotected C15-epimerized triol 53. We believe this epimerization occurred as the diol moiety was deprotected via *o*-quinone methide formation.

A selective protection of triol 53 then furnished silyl ether 54. Subsequent dearomatization of 54 afforded dienone 55b as an inseparable mixture of C15 diastereomers in 33% yield, along with the undesired C19-epimer (55a) in 27% yield. Lei and co-workers have previously reported the conversion of dienone 55b to incarviate A (3) using tetrabutylammonium fluoride (TBAF). The  $^1\text{H}$  NMR of dienone 55b was in full agreement with the previously reported data.<sup>12</sup> Our access to 55b thus constitutes a formal synthesis of 3 that occurs in 10 steps from known 3,5-dibromo-2-pyrone (17) [or in the longest linear sequence of 16 steps from commercially available (*R*)-pulegone].

## CONCLUSION

In summary, in this article we have detailed various synthetic studies toward the divergent syntheses of delavatine A (1) and incarviate A (3). Our initial efforts focused on assembling the indane core that is shared by these natural products from both symmetric bis-coupled furan 12 and bis-coupled pyrone 19. To circumvent a problematic deprotonation of a highly acidic  $\alpha$ -vinyl hydrogen in methyl esters 22 and 23, the cyclopentenyl rings were differentiated by replacing one of the ester groups with an aldehyde substituent. This modification was critical to achieving the synthesis of delavatine A (1) and incarviate A (3). Key features of our synthetic route include (a) sequential Stille–Stille coupling followed by ring-opening with cyanide ion occurring in a single pot, (b) a cascade sequence involving five transformations (silyl enol ether formation, *E/Z* isomerization,  $6\pi$  electrocyclozation, desilylation, and aromatization) occurring in a single pot, and (c) the first reported access to the putative biogenetic precursor (2). While all our efforts to convert the biosynthetic common intermediate to incarviate A (3) were unsuccessful, we achieved a formal synthesis of 3 from an alternative common intermediate, thus developing a divergent synthetic route to access 1 and 3. Overall, our studies culminated in the development of a symmetry-inspired, concise, and modular approach to 1 and 3, which has set the stage for the synthesis of a library of structurally related analogues to unravel the biological properties of these natural products.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b07693.

Experimental details and spectroscopic data (PDF)

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## Notes

The authors declare no competing financial interest.

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