A Unified Strategy for the Enantiospecific Total Synthesis of Delevatine A and Formal Synthesis of Incarviatone A

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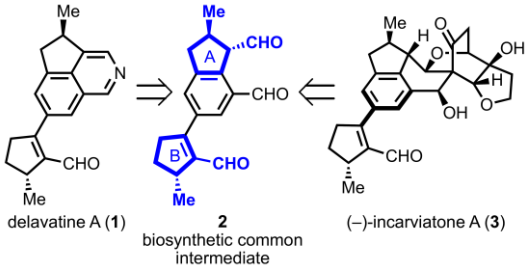
Introduction

Delevatine A and incarviatone A are natural products recently isolated from plants of *Incarvillea*, which has been found to be important in medicines and pharmaceuticals. Since the studies of its valuable utility, various synthetic protocols to access those compounds have been developed, which are completed independently. Given the fact that past developed protocols to those two natural products remain separate and different, it is highly desirable to develop a unified synthetic method towards both compounds. Herein, the authors proposed 3,5-dibromo-2-pyrone (**2**) as a key building block, which is plausible to derive both delevatine A (**1**) and incarviatone A (**3**).

Results & Discussions

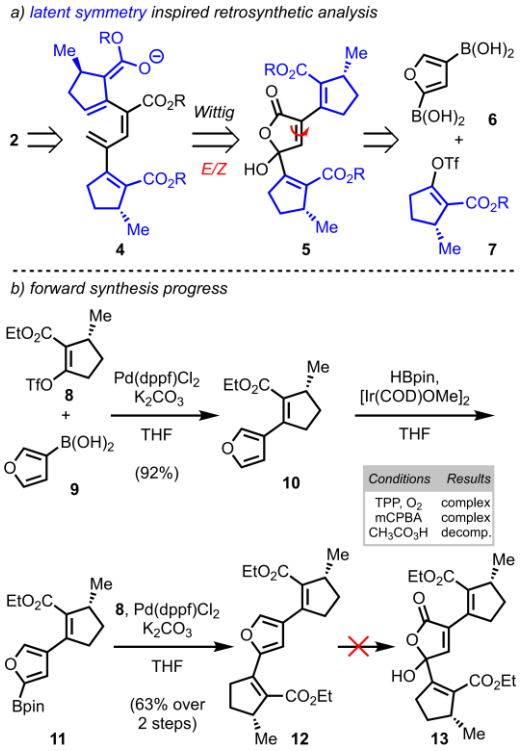
Scheme 1. A synthetically plausible intermediate **2** derives **1** and **3**

Inspired by a known biosynthetic route access to **1** and **3** starting from a key intermediate **2**, the authors hypothesized that **1** and **3** could also be derived from **2** in synthetic chemistry, which would demonstrate a unified and step-economical synthetic method to those two valuable natural products.



Scheme 1.

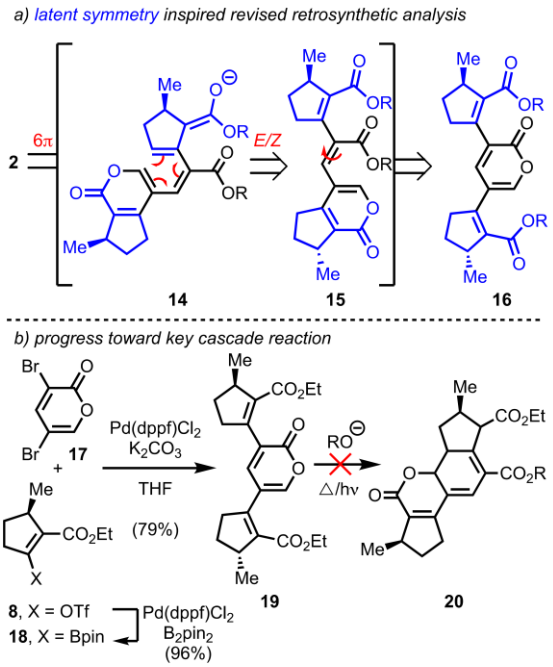
Scheme 2. Initial retrosynthetic analysis of **2** & Synthetic strategy to **13**



According to the structure of **2**, the authors hypothesized **2** might be synthesized from **4** via 6π electrocyclization to form a benzene core in the middle. Moreover, **5** is the oxidative product of cross coupling of **6** and **7**, and **4** could be derived from **5** via *E*/*Z* isomerization followed by a Wittig reaction. Unfortunately, the furan core of cross coupling product **12** is failed to be oxidized.

a) Initial retrosynthetic analysis of **2**:
4 to **2**: 6π Electrocyclization
5 to **4**: *E*/*Z* isomerization & Wittig reaction
6 + **7** to **5**: Pd-catalyzed cross coupling
b) Synthetic strategy to **13**:
8 + **9** to **10**: Pd-catalyzed cross coupling
10 to **11**: Ir-catalyzed C(sp^2)–H borylation of furan
11 to **12**: Pd-catalyzed cross coupling
12 to **13**: Oxidation of furan core(failed)

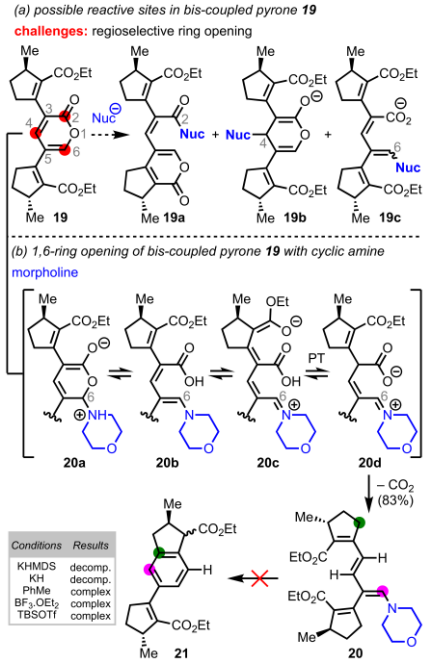
Scheme 3. Further retrosynthetic analysis of **2** & Synthetic strategy to **20**



Given the failure in **Scheme 2.**, the authors designed another plausible **14**, which might form **2** via 6π electrocyclization. **14** also could be derive from highly conjugated polyene **15** upon isomerization. Moreover, in the presence of an alkoxide nucleophile, bis-coupled pyrone **16** would give **15** as a ring opening product. Unfortunately, anticipated pericyclic product **20** is failed to form under both thermal and photolytic conditions.

a) Further retrosynthetic analysis of **2**:
14 to **2**: 6π Electrocyclization
15 to **14**: *E*/*Z* isomerization
16 to **15**: Ring-opening reaction
b) Synthetic strategy to **20**:
8 to **18**: Substituted borylation of triflate
17 + **18** to **19**: Pd-catalyzed Suzuki coupling
19 to **20**: Ring opening by alkoxide (failed)

Scheme 4. Investigations of nucleophile of **19**



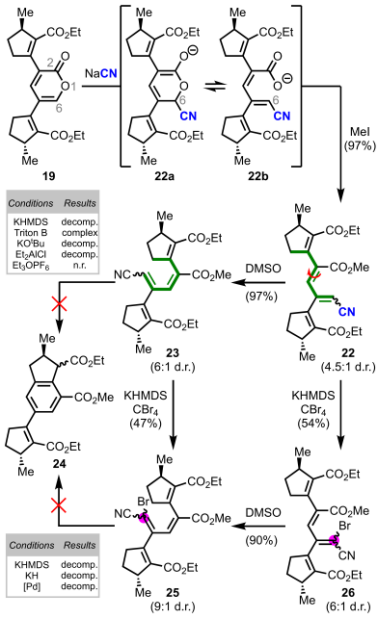
The authors observed the desired ring opening upon treating with morpholine, a cyclic amine. However, **20d** bears a carboxylate group which connected to a C(sp^3) atom, such structure undergoes a rapid decarboxylation to give **20**. Because the carboxylate group is essential to access either of the targeted natural products **1** or **3**, this route was ultimately unworkable.

a) Nucleophile investigation for **19**

Three spots in **19** (C2, C4, C6) were considered as being attacked when treated with various nucleophiles, giving **19a** (C2), **19b** (C4), and **19c** (C6) respectively.

b) 1,6-Ring opening of **19** with morpholine

Scheme 5. Ring opening of **19** with NaCN



Given the failure in **Scheme 4.** with morpholine, the author employed NaCN to investigate the ring opening. Delightfully, treating with NaCN also gave the corresponding ring opening product **22b**, which bears a carboxylate group connected to a C(sp^2) atom. Unlike the case of **20d**, **22b** could suffer undesired decarboxylation and be easily trapped by iodomethane to give methyl ester **22**.

The authors treated **23** with KHMDS in CBr_4, bromination occurred on vinyl moiety, which indicated a priority that deprotonation on vinyl group occurs rather than is on the γ-position of α,β-unsaturated ester moiety. Bromination also occurred while treating **22** with KHMDS in CBr_4, indicated the same priority.

19 to **22**: Ring opening treating with NaCN

22a to **22b**: 6π Electrocyclization

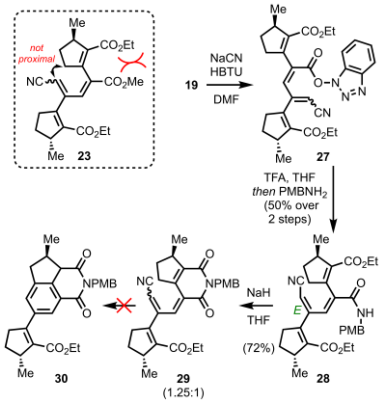
22b to **22**: Methylation of carboxylate group (Methyl ester formation)

22 to **23**, **26** to **25**: *E*/*Z* isomerization

22 to **26**, **23** to **25**: Bromination of vinyl moiety

23/**25** to **24**: 6-*endo*-trig Michael-type addition (failed)

Scheme 6. Ester moiety-locking strategy towards **30**



The authors considered the steric clash between two ester moieties in **23** might distance the vinyl nitrile group from the γ-position of the α,β-unsaturated ester moiety. Thus, the interaction of two ester moieties might be the reason for the failure of Michael addition to give **24**. Herein, the authors attempted to lock ester moieties to decrease the interaction, aiming to facilitate desired Michael-type addition. Unfortunately, it was ultimately failed.

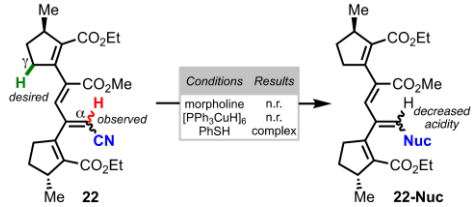
19 to **27**: Ring opening with NaCN followed by HBTU substitution

27 to **28**: *E*/*Z* Isomerization followed by PMB introduction with $PMBNH_2$

28 to **29**: Cyclization by NaH to lock ester moieties.

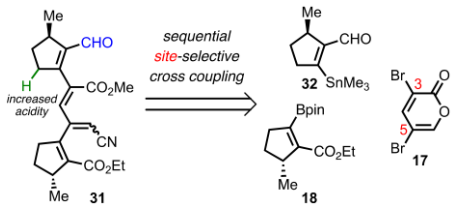
29 to **30**: 6-*endo*-trig Michael-type addition (failed)

Scheme 7. Acidity decreasing substitution of CN group in **22**



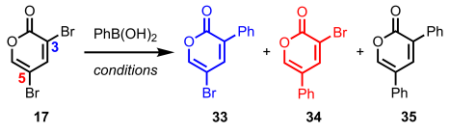
Since the strategy by locking ester moieties is failed, the authors considered two plausible methods to modify the priority: a) by substitute the cyanide group on the vinyl moiety with an appropriate substituent to decrease the acidity or b) to increase the acidity of hydrogen atom in gamma-position. Herein, the authors firstly tested the former hypothesis. Unfortunately, all **22-Nuc** were failed, giving a result as returning to **22** or turning to complex mixture.

Scheme 8. Retrosynthetic analysis of **31**



Since the former method is failed, the authors chose the latter strategy, to increase the acidity of γ-position hydrogen atom of α,β-unsaturated ester moiety by introducing an electron-withdrawing group into the cyclopentane moiety. If reaction goes as expected, **31** could be derived from **17** and **32** as well as **18** via cross coupling reaction. Herein, the authors investigated the regioselectivity of **17** during Suzuki coupling reaction, since **17** bears a dibromo-substituted structure. (see **Table 1.**)

Table 1. Conditions optimization of Suzuki coupling with **17**



		yield[b] (%) **33**:**34**:**35**			
ε[a]	Solvent	With CuI 23 °C	With CuI Δ	Without CuI 23 °C	Without CuI Δ
47	DMSO	nd:12:nd	8:13:nd	nr	—[c]
38.25	DMF	nd:18:nd	15:37:nd	nr	tr:nd:nd
21.01	acetone	tr:32:nd	16:29nd	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

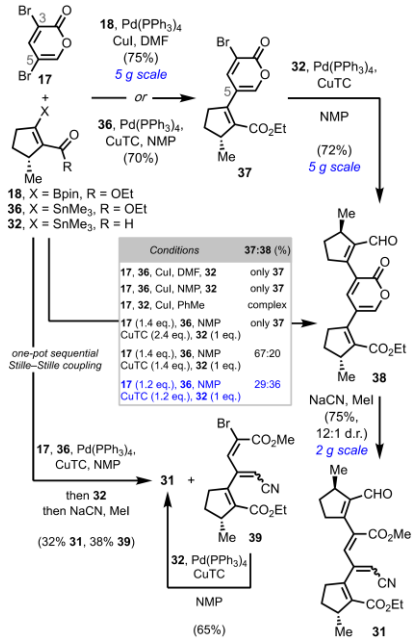
increasing polarity

[a]Dielectric constant at 20 °C.[38] [b]Determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard. [c]Decomposition of **17**. Conditions: PhB(OH)$_2$ (1.2 equiv), Pd(PPh$_3$)$_4$ (10 mol %), CuI (1.0 equiv), K$_2$CO$_3$ (2.0 equiv), solvent (0.1 M). nd = not detectable, tr = trace, and nr = no reaction.

3,5-Dibromo pyrone **17** was treated with PhB(OH)$_2$ under various conditions, including treating under room temperature or heating, testing with solvents bearing different polarity, and the presence or absence of copper (II) iodide. Ultimately, three facts have been understood through these outcomes:

1. With the polarity of solvent increasing, selectivity to **34** (C3) goes higher.
2. Reaction rate is irrelative with reaction temperature.
3. Presence of copper (II) iodide enables reaction under room temperature.

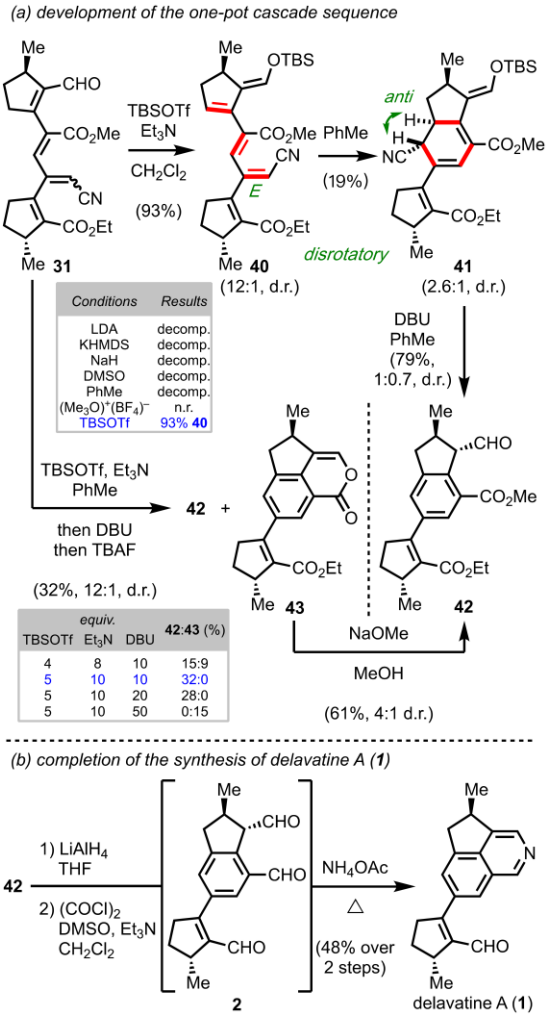
Scheme 9. Synthesis route to **31**



Given the fact through the outcomes in **Table 1.** including C3 atom reacts rather than C5 in **17**, the authors achieved the synthesis of targeted product shown in **Scheme 8.** through various cross coupling reactions. One-pot synthesis has also been achieved via sequential Stille-Stille coupling reactions, which shown the step-economy.

17 to **37** with **18**: Suzuki coupling;
with **36**: Stille coupling
37 to **38** with **32**: Stille coupling
38 to **31**: Nucleophilic substitution by NaCN
17 to **38** could be completed in one step:
17 to **38** with **32** and **36**: Stille coupling
Also, one-spot synthesis has been investigated.
17 to **31** with **36**: Stille coupling; then **32**: Stille coupling
Compound **39** was also obtained as side product, to convert it to **31**:
39 to **31** with **32**: Stille coupling

Scheme 10. Completion of the synthesis of **1** from **31**



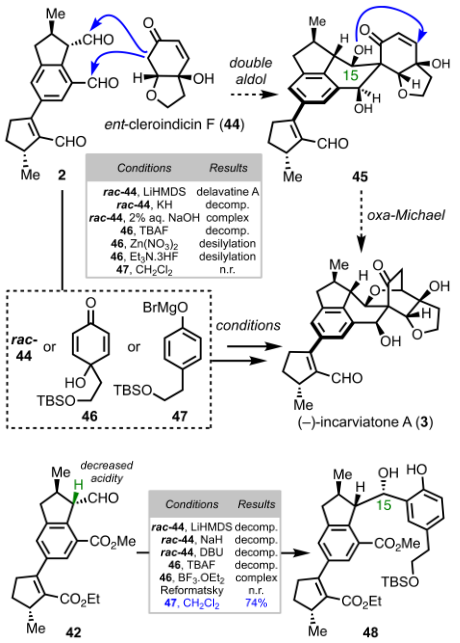
With **31** which bears a modified structure with increased acidity in hand, the authors treated **31** under base condition. Delightfully, deprotonation occurred in the γ-position hydrogen atom of α,β-unsaturated ester moiety **31**, giving enolate **40**. Following by a 6π electrocyclization, **41** was formed then treated with DBU in toluene, gave **42** which is the precursor of **2**.

Also, one-pot synthesis has been achieved here under the same conditions as in the step-by-step route. However, **43** was generated as side product under one-pot conditions, which could be converted to **42** easily by treating with NaOMe in MeOH.

42 could derive key intermediate **2** by treating with LiAlH$_4$ to be converted to a thiol and then oxidized. **2** was treated *in situ* with NH$_4$OAc to provide delavatine A (**1**).

40: *E*/*Z* isomerization
40 to **41**: 6π Electrocyclization
41 to **42**: Aromatization with elimination of HCN
Also, one-spot synthesis has been investigated.
31 to **42** with **40**: *E*/*Z* isomerization followed by 6π electrocyclization, then aromatization with elimination of HCN
Compound **43** was also obtained as side product, to convert it to **42**:
43 to **42**: Nucleophilic attack by sodium methoxide (NaOMe)
42 to **2**: Reduction to thiol by LiAlH$_4$, then Swern oxidation with (COCl)$_2$
2 to **1**: Leuckart reaction by NH$_4$OAc to convert aldehyde to amine

Scheme 11. Hypothesis inspired by the biosynthesis of **3**



Biosynthetically, **3** could be derived via *oxa*-Michael addition of **45**, which could be formed by a double aldol reaction from **2**. However, unlike in nature, such route is extremely complicated in synthetic chemistry with facing chemo-, regio- and enantioselective problems.

Inspired by the biosynthesis route as well as the structure of corresponding intermediate **45**, the authors described a key intermediate **48**, which is similar to **45** and derived from **42**.

Under investigations of various conditions, only the case with the treatment of **47** in CH_2Cl_2 gave **48** in 74% yield, since all other conditions were failed with decomposition or complex mixture as an outcome.

42 to **48**: Nucleophilic addition by enolate **47**

Scheme 12. Completion of the **formal** synthesis of **3** from **48**

48 to **49**: Acetal preparation (diol protection)

49 to **50**: Reductiion by DIBAL-H followed by Swern oxidation

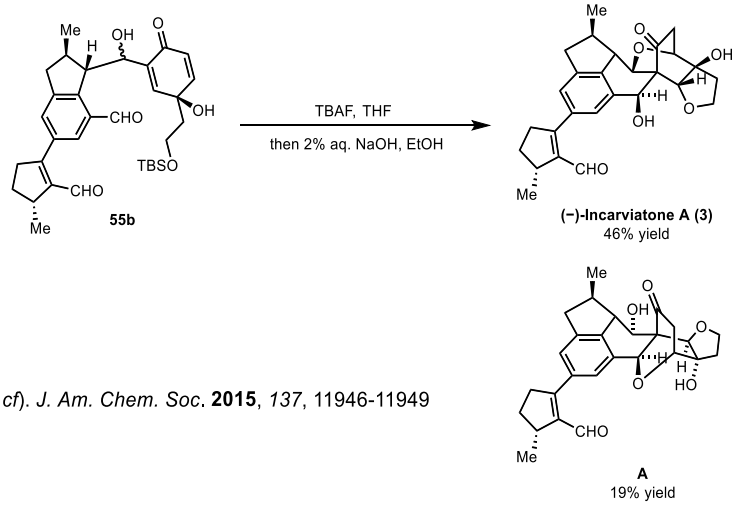
50 to **51**: Acetal deprotection followed by nucleophilic attack

50 to **52**: Acetal preparation by PPTS

52 to **53**: Deprotection of acetal by HCl

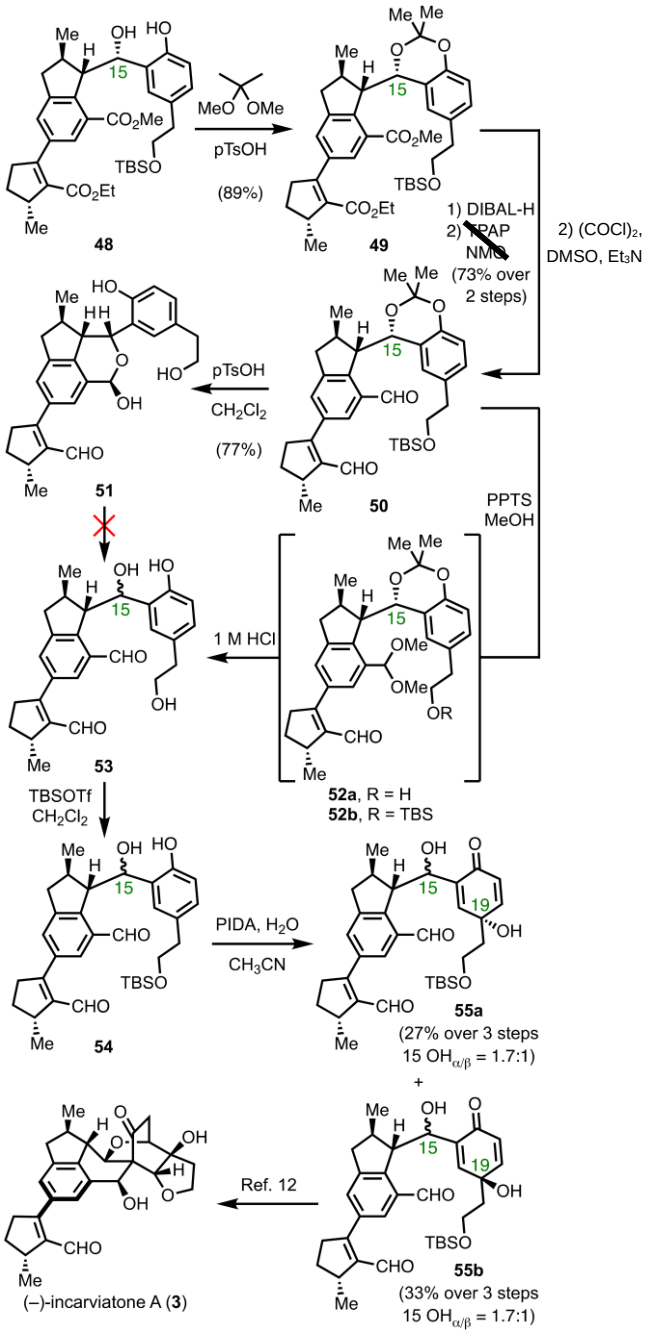
53 to **54**: TBS group introduction

54 to **55a/55b**: Oxidative dearomatization with PIDA



cf). *J. Am. Chem. Soc.* **2015**, *137*, 11946-11949

Figure 1.



Scheme 12.

Figure 1. Completion of **3** via one-pot synthesis from **55b**

55b is a synthetic precursor to (−)-incarviatone A. In 2015, Lei and co-workers reported the total synthesis of **3** via the same intermediate **55b**. Herein the route from **55b** to **3** written in Lei's paper is shown. **3** was obtained in 46% with **A** in 19% yield as a by-product.

Conclusion

The authors have developed a unified strategy for the synthesis of delavatinde A and incarviatone A. The key step is to synthesize a key building block **2**, which is inspired by the biosynthesis route of those natural products.

The accomplishment of the synthesis has set the stage for the synthesis of structurally related compounds, demonstrate the value of the development of a step-economical synthetic method.