



# Studies toward the AB ring system of the tetrapetalone natural products



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## ABSTRACT

Synthetic efforts toward the rapid assembly of the AB ring system of the tetrapetalones is described. Key to this work was the use of [3+2] cycloaddition/oxidative extrusion methodology to furnish functionalized aryl enones. The Nazarov cyclization of these substrates was examined, and optimized to generate the AB ring carbon skeleton. Then, Pd-catalyzed cross-coupling were conducted, and conditions were identified that enabled installation of the requisite C14–N bond.

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## 1. Introduction

In 2003, Hirota and co-workers isolated tetrapetalone A (**1**, Fig. 1) from a *Streptomyces* culture broth, and this natural product was found to inhibit soybean lipoxygenase (SLO).<sup>1,2</sup> Tetrapetalones B (**2**), C (**3**), and D (**4**) were also isolated from a *Streptomyces* culture extract in a separate report, and these natural products were also found to inhibit SLO.<sup>3</sup> Since the catalytic domain of plant and mammalian lipoxygenases is highly conserved,<sup>4</sup> the study of an SLO inhibitor like tetrapetalone A could lead to the identification of new human lipoxygenase (HLO) inhibitors. HLOs catalyze the first step

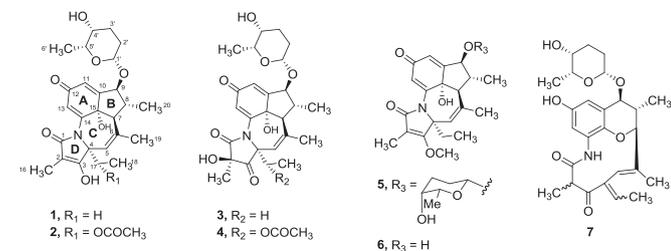
in the conversion of arachidonic acid to the leukotrienes, which are signaling molecules implicated in several inflammatory diseases.<sup>5</sup>

The SLO inhibition of the tetrapetalones was moderate, but comparable to known SLO inhibitors kojic acid and nordihydroguaiaretic acid (NDGA) (Table 1).<sup>3,6</sup> However, when tetrapetalone A was derivatized to tetrapetalone A-Me (**5**) via treatment of **1** with diazomethane, all SLO inhibitory activity was eliminated (entry 5).<sup>6</sup> **5** was subjected to acidic hydrolysis to furnish tetra-

**Table 1**

Inhibitory activities of **1–5** against soybean lipoxygenase

Compound	IC <sub>50</sub> (μM)
<b>1</b>	190–460
<b>2</b>	320
<b>3</b>	360
<b>4</b>	240
<b>5</b>	>1000
Kojic acid (positive control)	110–280
NDGA (positive control)	190–290



**Fig. 1.** Structures of tetrapetalones A–D, derivatives, and ansaetherone.

petalone A-Me aglycon (**6**), and the absolute configuration of this material was determined by the preparation of Mosher esters.<sup>6</sup> Hirota and co-workers also discovered the radical scavenger ansaetherone (**7**) present in a *Streptomyces* culture extract, and theorized that it could be an intermediate in the biosynthesis of the tetrapetalones.<sup>7</sup>

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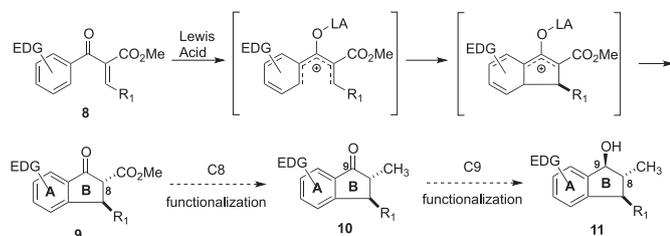
The tetrapetalone natural products possess a  $\beta$ -D-rhodinose moiety connected to a tetracyclic core with unprecedented complexity. Key features of this core include a *para*-quinol A ring, a five-membered B ring containing four contiguous stereogenic centers, a 7-membered C ring containing a bridging trisubstituted olefin, and a tetramic acid D ring. Furthermore, a study whereby *Streptomyces* were fed  $^{13}\text{C}$ -enriched building blocks revealed that the rhodinose moiety is derived from glucose, the A ring is derived from 3-amino-5-hydroxybenzoic acid, and the remainder of the molecule is constructed from propanoate and butanoate building blocks, probably by the action of polyketide synthase.<sup>8</sup>

To date, a total synthesis of tetrapetalone A has not been reported, though several laboratories have published synthetic approaches. The first report appeared in 2005 by Porco and co-workers, who sought to test a biosynthetic hypothesis: the tetracyclic core was formed through an oxidative transannular [4+3] cyclization of an ansa-bridged macrocycle.<sup>9a</sup> While the group initially reported the success of this strategy, a later disclosure indicated that while oxidation had been successful, the cycloaddition had not.<sup>9b</sup> In 2010, Sarpong and co-workers published an approach that culminated in the first synthesis of the tetracyclic skeleton of the tetrapetalone system.<sup>10</sup> In brief, they constructed the AB ring system via Nazarov cyclization, ABD ring system via Paal-Knorr methodology, and the ABCD ring system via an oxidation/Friedel–Crafts acylation/oxidation cascade.<sup>10</sup> Two other approaches toward the tetrapetalone core have been published by Hong (2009)<sup>11</sup> and Pettus (2014).<sup>12</sup>

In 2014, our group reported the first synthesis of tetrapetalone A-Me aglycon (**6**).<sup>13</sup> Herein is an account of our early work on the project, detailing Nazarov cyclization studies targeting the indanone precursor to the AB ring system, and the installation of the C14–N bond of the A ring.

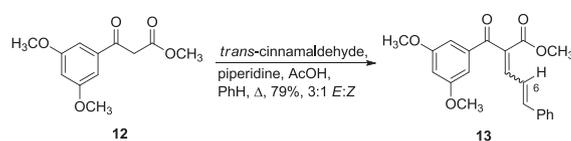
## 2. Results/discussion

From the outset, we planned to construct the AB ring system using a polarized Nazarov cyclization on a substrate resembling aryl enone **8**, to form bicycle **9** (Scheme 1).<sup>14</sup> This strategy would allow us to convert the aromatic A ring into a *para*-quinol in a late-stage transformation, and the  $\beta$ -ketoester to a cyclopentane with the requisite C9 alkoxy group and C8 methyl group. Based on our earlier work on cyclizations of polarized aromatic systems,<sup>15</sup> and Sarpong's study of a closely related cyclization,<sup>16</sup> we expected the cyclization to be possible, but perhaps difficult to achieve catalytically, and certainly difficult to achieve enantioselectively.



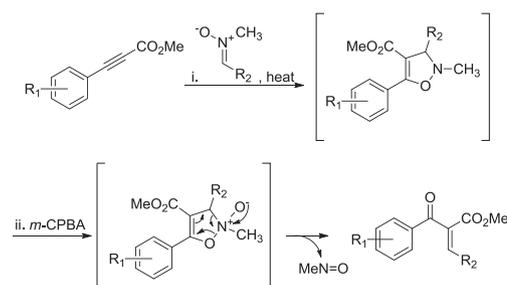
**Scheme 1.** Outline of the polarized Nazarov cyclization in the context of AB ring construction.

Over the course of our investigations on the tetrapetalone ring system, we prepared and cyclized a number of different aryl vinyl ketones. Aryl vinyl ketone **13** was easily prepared utilizing a Knoevenagel condensation protocol previously reported in our group (Scheme 2).<sup>14</sup> However, Knoevenagel condensation of  $\alpha$ -methyl-*trans*-cinnamaldehyde with  $\beta$ -ketoester **12** failed.



**Scheme 2.** Aryl enone synthesis via Knoevenagel condensation.

We solved this problem by employing a different method previously explored in our group for the mild construction of aryl enones.<sup>14b,17</sup> As shown in Scheme 3, alkynes of type **14** and nitrones of type **15** undergo [3+2] cycloaddition followed by oxidative chelotropic extrusion of nitrosomethane to furnish aryl enones of type **16**. The results are shown in Table 2. For example, the protocol furnished aryl enone **16a**, containing the requisite methyl group on C6, from alkyne **14a** and nitron **15a** (entry 1). This substrate could not be prepared using the Knoevenagel condensation protocol in Scheme 2. The olefin geometry of aryl enone **16a** was determined to be predominantly *Z* (>19:1 ratio), by examining the  $^3J$  coupling constants between the ketone carbon and the ester carbon with the C7 proton, which were obtained using selective proton-decoupled carbon NMR techniques.<sup>18</sup> In an attempt to prepare the aryl enone unsubstituted at the alkene terminus, which we thought would be optimal for subsequent C ring formation, nitron **15b** was tested in the cycloaddition, but it decomposed under the elevated thermal conditions. Fortunately, nitron **15c**, featuring a vinyl trimethylsilyl group, underwent smooth cycloaddition/extrusion (entry 3). The trimethyl silyl group stabilizes the nitron and serves as a protecting group for the desired 1,1-disubstituted alkene, as it is readily removed under acidic conditions (*vide infra*).



**Scheme 3.** [3+2] Cycloaddition/oxidative extrusion cascade for preparation of functionalized aryl enones.

**Table 2**  
Synthesis of aryl enones **16a–e** via [3+2] cycloaddition/oxidative extrusion cascade

Entry	R <sub>1</sub>	R <sub>2</sub>	Yield	dr
1	OTIPS ( <b>14a</b> )	Ph ( <b>15a</b> )	80% ( <b>16a</b> )	>19:1 ( <i>Z</i> : <i>E</i> )
2	OTIPS ( <b>14a</b> )	H ( <b>15b</b> )	—	—
3	OTIPS ( <b>14a</b> )	TMS ( <b>15c</b> )	nd <sup>a</sup> ( <b>16b</b> )	5:1
4	Br ( <b>14b</b> )	Ph ( <b>15a</b> )	85% ( <b>16c</b> )	>20:1
5	Br ( <b>14b</b> )	TMS ( <b>15c</b> )	79% ( <b>16d</b> )	1.7:1
6	Br ( <b>14b</b> )	TBS ( <b>15d</b> )	77% ( <b>16e</b> )	7.1:1

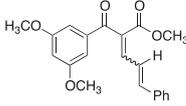
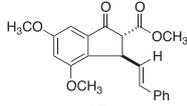
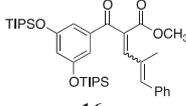
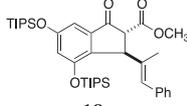
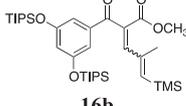
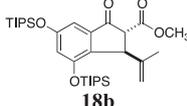
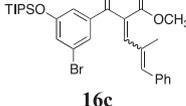
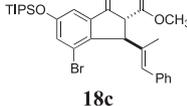
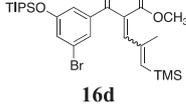
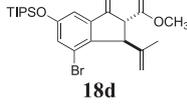
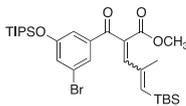
<sup>a</sup> Not determined. See Experimental section.

We also prepared aryl bromides **16c–e** (entries 4–6) using the [3+2] cycloaddition/chelotropic extrusion sequence. As in entries 1 and 3, nitrones **15a** and **15c** underwent the reaction cascade

smoothly (entries 4 and 5). The more robust vinyl *tert*-butyldimethylsilane was also prepared, as alternative protection for the 1,1-disubstituted alkene (entry 6).

With aryl dienones **13** and **16a–e** in hand, we could evaluate conditions for Nazarov cyclization (Table 3). Nazarov cyclization of **13** with catalytic Cu(OTf)<sub>2</sub> gave the *trans* cyclopentanone as the only detectable product in 81% yield (entry 1). A similar result was obtained with aryl enone **16a** using catalytic Cu(ClO<sub>4</sub>)<sub>2</sub> (entry 2). When aryl enone **16b** was subjected to Cu<sup>2+</sup> catalysis, cleavage of the TMS group occurred, presumably due to trace Bronsted acid present in the reaction mixture (entry 3).<sup>19</sup> This convenient desilylation facilitated the ring-closing metathesis studies that led to the formation of the C ring.<sup>15</sup> Indanone **18b** was isolated (in crude form) as a 3:1 mixture of *trans*:*cis* isomers (see experimental section).

**Table 3**  
Synthesis of indanones via Nazarov cyclization

#	Starting material	Conditions	Product	Yield; dr ( <i>trans</i> : <i>cis</i> )
1	 <b>13</b>	5 mol % Cu(OTf) <sub>2</sub> , DCE, 60 °C	 <b>17</b>	81%; >20:1
2	 <b>16a</b>	5 mol % Cu(ClO <sub>4</sub> ) <sub>2</sub> , DCE, 45 °C	 <b>18a</b>	75%; >20:1
3	 <b>16b</b>	5 mol % Cu(ClO <sub>4</sub> ) <sub>2</sub> , DCE, rt	 <b>18b</b>	nd <sup>a</sup> ; 3:1
4	 <b>16c</b>	cat. Sc(OTf) <sub>3</sub> /Li(ClO <sub>4</sub> ), DCE, 45 °C	 <b>18c</b>	81%; 3:1
5	 <b>16d</b>	cat. Sc(OTf) <sub>3</sub> /Li(ClO <sub>4</sub> ), DCE, 45 °C	 <b>18d</b>	— <sup>b</sup>
6	<b>16d</b>	(TMS)NTf <sub>2</sub>	<b>18d</b>	— <sup>b</sup>
7	<b>16d</b>	1.1 equiv AlCl <sub>3</sub> , DCE, 0 °C	<b>18d</b>	71%; 3.6:1
8	<b>16d</b>	1.1 equiv Sc(OTf) <sub>3</sub> , DCE, rt	<b>18d</b>	46%; 3.6:1
9	 <b>16e</b>	1.1 equiv AlCl <sub>3</sub> , DCE, 0 °C	<b>18d</b>	~70–75%; 3.6:1

<sup>a</sup> Not determined. See Experimental section.

<sup>b</sup> Decomposition.

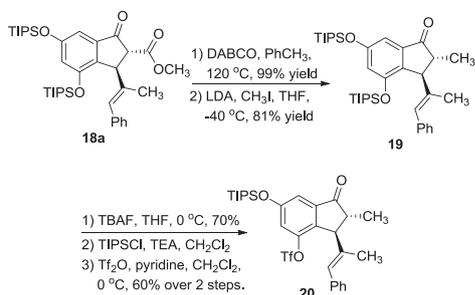
The inclusion of the electron-withdrawing bromide group on aryl enone substrates predictably reduced the reactivity of these substrates in the Nazarov cyclization reaction. For example, treatment of **16c** with catalytic Sc(OTf)<sub>3</sub> at 45 °C resulted in no reaction. It was only by using the Sc(OTf)<sub>3</sub>/Li(ClO<sub>4</sub>) catalyst combination (which we had used previously to cyclize other unreactive aryl enones)<sup>15</sup> that an 81% yield of **18c** could be obtained from **16c**, as a 3:1 mixture of *trans*:*cis* isomers (entry 4). Surprisingly, subjection

of **16d** to these conditions, or to (TMS)NTf<sub>2</sub>,<sup>20</sup> resulted in decomposition (entries 5 and 6). However, aryl enone **16d** did cyclize upon treatment with either superstoichiometric AlCl<sub>3</sub><sup>16</sup> (entry 7) or Sc(OTf)<sub>3</sub> (entry 8), furnishing indanone **18d**. As in entry 3, protodesilylation occurred under the reaction conditions.

We were curious to see whether the protodesilylation was contributing to the decomposition seen in the experiments in entries 5 and 6. Hence, we examined the Nazarov cyclization of aryl enone **16e**, with the assumption that its vinyl *tert*-butyldimethylsilyl group would not be cleaved as readily as a vinyl trimethylsilyl group. Unfortunately, attempts to catalyze the cyclization of **16e** with Sc(OTf)<sub>3</sub>/Li(ClO<sub>4</sub>), Cu(OTf)<sub>2</sub>/Li(ClO<sub>4</sub>), Al(OTf)<sub>3</sub>, and (TMS)NTf<sub>2</sub> all resulted in decomposition. As in entry 7, superstoichiometric AlCl<sub>3</sub> promoted the cyclization, affording indanone

**18d**. Thus, appending the bulkier TBS group on the vinyl terminus in place of the more labile TMS group did not appear to have any effect on the efficiency of the cyclization.

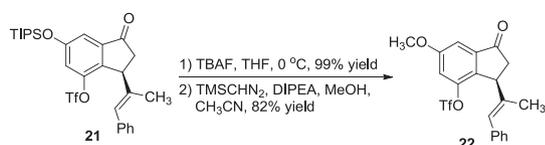
As shown in Scheme 4, indanone **18a** was functionalized (at C8) and converted to the aryl triflate in preparation for the anticipated installation of the C17–N bond via Buchwald–Hartwig cross-coupling. Thus, **18a** was decarbalkoxylated,<sup>21</sup> and methylated to furnish indanone **19** (Scheme 4). This material was then globally



**Scheme 4.** Transformation of **18a** to aryl triflate **20**.

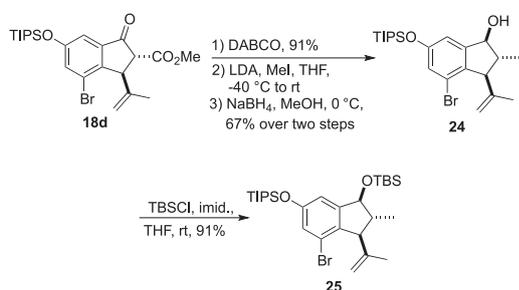
deprotected with TBAF, chemoselectively protected at the less hindered hydroxyl group, and then treated with triflic anhydride and pyridine to furnish aryl triflate **20**.

Aryl triflate **21** was synthesized following the reactions in [Scheme 4](#), except the C8 methyl group was not installed. This material was then deprotected with TBAF and methylated to furnish aryl triflate **22** ([Scheme 5](#)).

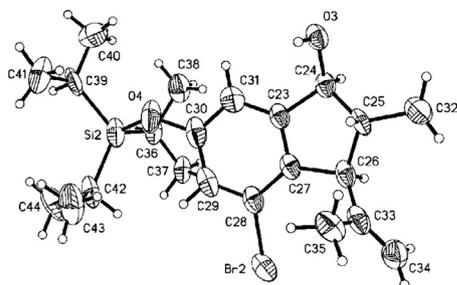


**Scheme 5.** Transformation of aryl triflate **21** to aryl triflate **22**.

As in [Scheme 4](#), indanone **18c** was subjected to decarboxylation to furnish aryl bromide **23**. Aryl bromide **25** was prepared in a similar fashion ([Scheme 6](#)). Indanone **18d** was decarboxylated, methylated, and reduced to furnish alcohol **24**, which was protected as the triisopropylsilyl ether. Importantly, both the C8 methylation and the reduction in [Scheme 6](#) were found to be diastereoselective, and the relative stereochemistry on the B ring was confirmed by single-crystal X-ray crystallography ([Fig. 2](#)). This relative stereochemistry also matched the desired stereochemistry present in the B ring of tetrapetalone A.



**Scheme 6.** Transformation of indanone **18d** to aryl bromide **25**.



**Fig. 2.** ORTEP diagram of alcohol **24**.

We originally planned to install the requisite C14–N bond using the powerful and versatile Buchwald–Hartwig cross-coupling technology ([Table 4](#)).<sup>22</sup> Initially, we tried the cross-coupling of aryl triflate **20** with lactam **26** (entry 1),<sup>23</sup> with no success. We next attempted cross-coupling with tertiary amine **27**, with a substitution pattern mapping onto C4 of tetrapetalone A. Our initial experiment again resulted in no reaction (entry 2), but use of the stronger base NaO<sup>t</sup>Bu resulted in detectable amounts of cross-coupled products (entry 3). It was clear that the poor results of these initial studies were due to the considerable steric hindrance of both coupling partners: the *ortho*-substituted aryl triflate and the tertiary amine.

To test this hypothesis, we attempted cross-coupling between aryl triflate **22** (containing the more robust methyl ether protecting group on C12) and the less sterically hindered amines **29** and **31** (entries 4 and 5). The result was a dramatic increase in the yield of the reaction. We also attempted the cross-coupling of the imine **33**<sup>24</sup> with aryl triflate **21**, which delivered the imine derivative **34** in modest yield (entry 6). Imine **34** could be hydrolyzed to the aniline (**35**) in 56% yield using aqueous acid.

In many instances, phenol byproducts arising from hydrolysis of the triflyl group were detected in the reactions in entries 1–6. To avoid this, we prepared aryl bromides to test in the cross-coupling reactions. First, we attempted the cross coupling of sterically hindered amine **27** with aryl bromide **23**. Unsurprisingly, no cross-coupled product was detected. We returned to the cross-coupling of imine **33**, which furnished aniline **35** in 27% yield after hydrolysis (entry 7). The next coupling partner we investigated was ammonia, which has essentially no steric hindrance. Using the protocol of Stradiotto,<sup>25</sup> we were able to cross-couple ammonia to aryl bromide **25** to furnish aniline **36** in 97% yield (entry 9). In a previous report, we successfully elaborated aniline **36** into tetrapetalone A-Me aglycon (**6**).<sup>13</sup>

### 3. Conclusions

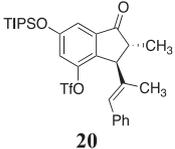
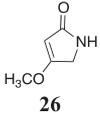
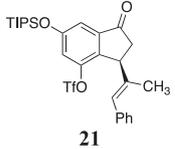
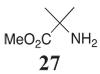
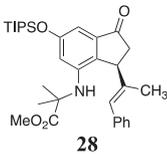
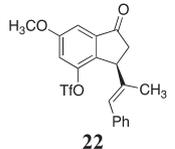
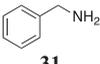
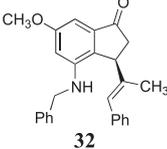
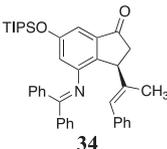
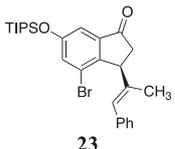
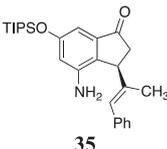
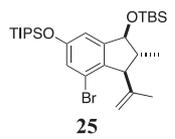
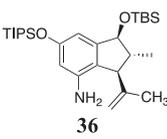
In summary, we have described our laboratory's strategies toward the synthesis of the AB ring of the tetrapetalones. We used three key steps to construct the important architectural features of the AB ring system. We first used a [3+2] cycloaddition between strategically functionalized alkynoates and nitrones, followed by oxidative extrusion of nitrosomethane to furnish aryl enones. Then, we used Nazarov cyclization on these aryl enones to form the AB ring carbon skeleton. Last, we used Pd-catalyzed cross-coupling to install the requisite C14–N bond. Ongoing work in our laboratory is focused on the completion of the total synthesis of tetrapetalone A, as well as synthesis of other tetrapetalone natural products, and evaluation of their biological activity.

## 4. Experimental section

### 4.1. General

All reactions were carried out under an argon or N<sub>2</sub> atmosphere in flame- or oven-dried glassware with magnetic stirring unless otherwise noted. Cold baths were prepared by mixing acetone/dry ice (−78 °C) or acetonitrile/dry ice (−40 °C). Reagents were used as obtained from commercial suppliers without further purification unless otherwise noted. Cu(ClO<sub>4</sub>)<sub>2</sub> was dried in a vacuum oven at 40 °C for 24 h, then ground and stored in a glovebox prior to use. Tetrahydrofuran, diethyl ether, methylene chloride, 1,2-dichloroethane, and toluene were purchased from Fisher and dispensed using the Glass Contour solvent purification system. Celite 545 was purchased from EMD. ACS grade hexanes and ethyl acetate were used for column chromatography. Thin layer chromatography (TLC) was performed on pre-

**Table 4**  
C14–N bond formation studies

#	Starting material	Conditions	Product	Yield
1	 <b>20</b>	 <b>26</b> K <sub>3</sub> PO <sub>4</sub> , Pd(PPh <sub>3</sub> ) <sub>4</sub> , Xantphos, dioxane, 110 °C	— <sup>a</sup>	— <sup>a</sup>
2	 <b>21</b>	 <b>27</b> Cs <sub>2</sub> CO <sub>3</sub> , Pd(OAc) <sub>2</sub> , BINAP, PhCH <sub>3</sub> , 105 °C	— <sup>a</sup>	— <sup>a</sup>
3	<b>21</b>	<b>27</b> NaO <sup>t</sup> Bu, 10% Pd(OAc) <sub>2</sub> , 20% BINAP, PhCH <sub>3</sub> , 105 °C	 <b>28</b>	— <sup>b</sup>
4	 <b>22</b>	 <b>29</b> K <sub>3</sub> PO <sub>4</sub> , 5% Pd <sub>2</sub> (dba) <sub>3</sub> , 10% DavePhos, PhCH <sub>3</sub> , 105 °C	 <b>30</b>	40%
5	<b>22</b>	 <b>31</b> Cs <sub>2</sub> CO <sub>3</sub> , 10% Pd(OAc) <sub>2</sub> , 15% BINAP, PhCH <sub>3</sub> , 100 °C	 <b>32</b>	50%
6	<b>21</b>	<b>33</b> HN=CPh <sub>2</sub> NaO <sup>t</sup> Bu, 3% Pd <sub>2</sub> (dba) <sub>3</sub> , 4.5% BINAP, PhCH <sub>3</sub> , 90 °C	 <b>34</b>	28%
7	 <b>23</b>	<b>33</b> NaO <sup>t</sup> Bu, Pd <sub>2</sub> (dba) <sub>3</sub> , BINAP, PhCH <sub>3</sub> , 110 °C; cat. HCl, THF, rt	 <b>35</b>	27%
8	 <b>25</b>	NH <sub>3</sub> NaO <sup>t</sup> Bu, [Pd(allyl)Cl] <sub>2</sub> , Mor-DalPhos, Dioxane, PhCH <sub>3</sub> , 90 °C	 <b>36</b>	97%

<sup>a</sup> No reaction.

<sup>b</sup> Trace amount of product detected.

coated silica gel 60 F<sub>254</sub> glass-supported plates from EMD, and visualization was performed with a UV lamp followed by staining with potassium permanganate, *p*-anisaldehyde, ninhydrin, or ceric ammonium molybdate solution followed by heating. Column chromatography was carried out on EM Science 60 Å silica gel (230–400 mesh). Chloroform-*d* and Methanol-*d*<sub>4</sub> was purchased from Cambridge Isotope Laboratories.

<sup>1</sup>H NMR spectra were recorded on a 400 MHz Bruker Avance spectrometer or a 500 MHz Bruker Avance spectrometer at room temperature. Chemical shifts are given in parts per million (ppm) from tetramethylsilane, referenced to solvent residual proton resonance ( $\delta=7.26$  for CHCl<sub>3</sub>,  $\delta=3.31$  for CH<sub>3</sub>OH). Some NMR spectra contain tetramethylsilane as an internal reference. NMR data are reported as: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=doublet of doublets, dq=doublet of quartets, br=broad), coupling constants (*J*) given in Hz, and integration. <sup>13</sup>C NMR spectra were recorded on a 100 MHz Bruker Avance spectrometer or a 125 MHz Bruker Avance spectrometer at room temperature with proton decoupling. Chemical shifts are given in parts per million (ppm) from tetramethylsilane, referenced to solvent carbon resonance ( $\delta=77.16$ ). Infrared spectra (IR) were recorded on a Shimadzu FTIR 8400S (ATR Mode) spectrometer or an ATI Mattson Genesis FTIR spectrometer. High resolution mass spectra (HRMS) were measured by the Chemistry Instrumentation Center of the University of Buffalo, Buffalo, NY 14260 or the Mass Spectrometry Lab of the University of Illinois, Urbana, IL 61801. X-ray crystallography data were collected by the X-ray Crystallographic Facility of the University of Rochester, Rochester, NY 14627.

## 4.2. Preparation of intermediates

**4.2.1.  $\beta$ -Keto ester **12**.** In a 25 mL round-bottom flask, potassium hydride (30% in mineral oil, 273.0 mg, 2.0 mmol) and sodium hydride (60% in mineral oil, 324.4 mg, 8.1 mmol) were washed with dry hexanes, then THF (4 mL) was added, followed by dimethylcarbonate (0.7 mL, 8.1 mmol), and a solution of commercially-available 3',5'-dimethoxy-acetophenone (730.7 mg, 4.1 mmol) in THF (5 mL). The reaction was stirred in a 65 °C oil bath for 2 h, cooled, then quenched with water (20 mL). The layers were separated, and the aqueous layer was extracted with ether (3×10 mL). The organic phases were combined and dried over MgSO<sub>4</sub>, filtered, and concentrated. The crude material was purified by column chromatography (8:1 hexanes:ethyl acetate), yielding 619.7 mg (64%) of **12**. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.04 (d, *J*=2.1 Hz, 1H), 6.65 (s, 1H), 3.95 (s, 2H), 3.80 (s, 6H), 3.73 (s, 3H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  192.16, 167.95, 161.03, 137.84, 106.34, 106.03, 55.66, 52.55, 45.85.

**4.2.2. Aryl enone **13**.** In a 50 mL round-bottom flask, a solution of  $\beta$ -ketoester **12** (619.7 mg, 2.6 mmol) in benzene (12 mL) was combined with piperidine (30  $\mu$ L, 0.3 mmol), acetic acid (90  $\mu$ L, 1.6 mmol), and *trans*-cinnamaldehyde (0.4 mL, 2.9 mmol). The flask was fitted with a Dean–Stark trap, and refluxed for 16 h. The reaction was cooled, diluted with benzene, and washed with NH<sub>4</sub>Cl (50 mL), NaHCO<sub>3</sub> (50 mL), and brine (25 mL). The organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated. The crude material was purified by column chromatography (8:1 hexanes:ethyl acetate), yielding 677.3 mg (74%) of **13**. Characterized as a mixture, *E:Z*=3:1, following the procedure of Ref. 18; *E* isomer: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.73–7.67 (m, 1H), 7.43–7.35 (m, 5H), 7.08 (d, *J*=2.3 Hz, 2H), 7.02 (s, 1H), 6.76 (dd, *J*=15.4, 11.8 Hz, 1H), 6.69 (t, *J*=2.3 Hz, 1H), 3.84 (s, 6H), 3.74 (s, 3H). *Z* isomer: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.79 (dd, *J*=15.5, 11.5 Hz, 1H),

7.57 (d, *J*=1.8 Hz, 1H), 7.34–7.28 (m, 5H) 7.20 (d, *J*=11.5 Hz, 1H), 6.96 (d, *J*=2.3 Hz, 2H), 6.67 (t, *J*=2.3 Hz, 1H), 3.84 (s, 6H), 3.77 (s, 3H).

**4.2.3. Alkynoate **14a**.** Prepared according to Ref. 17. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.70 (d, *J*=2.4 Hz, 2H), 6.52 (t, *J*=2.4 Hz, 1H), 3.83 (s, 3H), 1.24 (m, 6H), 1.10 (d, *J*=9.0 Hz, 36H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  157.0, 154.5, 120.3, 117.5, 115.3, 86.6, 79.6, 52.7, 17.4, 12.6; IR (neat, cm<sup>-1</sup>): 2943.7, 2891.1, 2866.5, 2218.9, 1715.6, 1577.7, 1462.4, 1427.2, 1241.6.

**4.2.4. Alkynoate **14b**.** Prepared according to Ref. 13. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.31–7.29 (m, 1H), 7.12 (t, *J*=2.0 Hz, 1H), 7.01–6.97 (m, 1H), 3.83 (s, 3H), 1.31–1.18 (m, 3H), 1.09 (d, *J*=7.3 Hz, 18H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  156.89, 154.26, 128.45, 126.25, 122.83, 122.67, 121.92, 84.63, 80.89, 53.04, 17.94, 12.69; IR (neat, cm<sup>-1</sup>): 2947, 2866, 2230, 1717, 1586, 1555, 1462, 1424, 1319, 1292, 1231, 1196, 1157, 976, 883, 853, 810, 733, 675, 648, 621; HRMS (ESI): Calculated for C<sub>19</sub>H<sub>28</sub>BrO<sub>3</sub>Si ([M+H]<sup>+</sup>): *m/z* 411.0991, found: 411.0990.

**4.2.5. Nitron **15a**.** Prepared according to Ref. 17. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.26 (s, 1H), 7.36–7.34 (m, 5H), 6.93 (s, 1H), 3.79 (s, 3H), 2.19 (s, 3H).

**4.2.6. Nitron **15b**.** Prepared according to Ref. 17. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.83 (s, 1H), 6.57 (s, 1H), 5.39 (s, 1H), 3.73 (s, 3H), 1.99 (s, 3H).

**4.2.7. Nitron **15c**.** Prepared according to Ref. 13. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  6.90 (s, 1H), 6.80 (s, 1H), 3.68 (s, 3H), 2.09 (s, 3H), 0.14 (s, 9H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  142.15, 138.07, 137.20, 54.46, 20.95, -0.20. IR (neat, cm<sup>-1</sup>): 2955, 2897, 1562, 1416, 1385, 1304, 1246, 1177, 1153, 1026, 961, 918, 833, 768, 748, 691, 644; HRMS (ESI): Calculated for C<sub>8</sub>H<sub>18</sub>NOSi ([M+H]<sup>+</sup>): *m/z* 172.1158, found: 172.1155.

**4.2.8. Nitron **15d**.** Prepared in analogy to **15c**. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.87 (s, 1H), 6.86 (s, 1H), 3.71 (s, 3H), 2.14 (s, 3H), 0.91 (s, 9H), 0.13 (s, 6H).

**4.2.9. Aryl enone **16a**.** In a dry 100 mL round-bottom flask was weighed the nitron **15a** (1.40 g, 8.0 mmol), **14a** (3.6 g, 7.1 mmol), and toluene (35 mL), and the solution was heated at 80 °C for 16 h. The solution was concentrated, and CH<sub>2</sub>Cl<sub>2</sub> (35 mL) was added, cooled to -20 °C, and *m*-CPBA (2.5 g, 11.6 mmol) was added and stirred for 30 min. The reaction was quenched with saturated Na<sub>2</sub>SO<sub>3</sub> (50 mL), the layers were separated and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2×50 mL), the organic phases were combined and washed with brine (50 mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude material was purified by column chromatography (8:1 hexanes:ethyl acetate), yielding 3.0 g (65%) of **16a**. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.66 (d, *J*=0.8 Hz, 1H), 7.36–7.34 (m, 5H), 7.07 (d, *J*=2.4 Hz, 2H), 6.98 (s, 1H), 6.65 (t, *J*=2.0 Hz, 1H), 3.69 (s, 3H), 1.79 (s, 3H), 1.30–1.16 (m, 6H), 1.12 (d, *J*=9.0 Hz, 36H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  195.0, 165.8, 157.3, 147.8, 141.9, 138.9, 136.2, 133.3, 129.7, 129.2, 128.3, 128.0, 117.3, 113.7, 52.3, 17.8, 12.5; IR (neat, cm<sup>-1</sup>): 3023.7, 2944.7, 2892.3, 1724.2, 1713.6, 1678.6, 1672.0, 1587.8, 1442.8, 1333.8, 1249.2, 1197.6; HRMS (EI) calculated for C<sub>38</sub>H<sub>58</sub>O<sub>5</sub>Si<sub>2</sub> 650.3817, found 650.3817. <sup>3</sup>J<sub>C–H</sub>=4.2 Hz for C<sub>ketone</sub>-H, <sup>3</sup>J<sub>C–H</sub>=7.5 Hz for C<sub>ester</sub>-H.

**4.2.10. Aryl enone **16b**.** In a dry 100 mL round-bottom flask was weighed the nitron **15c** (0.33 g, 1.94 mmol), **14a** (0.5 g, 1 mmol),

and toluene (5 mL), and the solution was heated at 80 °C for 16 h. The solution was concentrated, and CH<sub>2</sub>Cl<sub>2</sub> (35 mL) was added, cooled to –20 °C, and *m*-CPBA (0.38 g, 1.7 mmol) was added and stirred for 30 min. The reaction was quenched with saturated Na<sub>2</sub>SO<sub>3</sub> (10 mL), the layers were separated and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2×10 mL), the organic phases were combined and washed with brine (10 mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude material was used for the next step. **16b** was characterized as two isomers (5:1) <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.46 (d, *J*=0.8 Hz, 1H, maj. isomer), 7.04 (d, *J*=2.0 Hz, 1H, maj. isomer), 6.89 (s, 1H, min isomer), 6.80 (s, 1H, min isomer), 6.61 (s, 1H, min isomer), 6.65 (s, 1H, maj. isomer), 6.10 (s, 1H, maj. isomer), 5.97 (s, 1H, min isomer), 3.83 (s, 3H, min isomer), 3.67 (s, 3H, maj. isomer), 1.98 (s, 3H, min isomer), 1.69 (s, 3H, maj. isomer), 1.26–1.21 (m, 6H, both isomers), 1.11–1.09 (m, 36H, both isomers), 0.16 (s, 9H, min isomer), 0.09 (s, 9H, maj. isomer); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 194.9, 165.8, 157.3, 156.9, 149.6, 148.1, 146.9, 145.8, 145.3, 138.8, 129.0, 117.3, 115.8, 113.7, 52.3, 29.7, 19.7, 17.9, 17.8, 12.6, –0.5, –0.6; IR (neat) 2945, 2867, 1726, 1678, 1585, 1461, 1439, 1332, 1237, 1168, 1028, 998 cm<sup>–1</sup>; HRMS *m/z* calcd for C<sub>35</sub>H<sub>63</sub>O<sub>5</sub>Si<sub>3</sub> (M+H<sup>+</sup>) 647.3978, found 647.3981.

**4.2.11. Aryl enone 16c.** To a 10 ml round-bottom flask was added **14b** (0.617 g, 1.5 mmol), **15a** (0.289 g, 1.65 mmol, 1.1 equiv), and toluene (5 ml). The flask was purged with argon for 10 min and heated at 80 °C overnight. The reaction mixture was concentrated under reduced pressure. To a 10 ml round-bottom flask was added the crude material (0.75 g, 1.28 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (5 ml). The flask was cooled to 0 °C. *m*-CPBA (77%, 0.8625 g, 5 mmol, 3 equiv) was added and the reaction mixture was stirred for 30 min. The reaction mixture was quenched with a saturated aqueous solution of Na<sub>2</sub>SO<sub>3</sub>, extracted with ether, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (9:1 hexanes:ethyl acetate) to afford **16c** (0.67 g, 94%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.70 (d, *J*=0.6 Hz, 1H), 7.69 (t, *J*=1.5 Hz, 1H), 7.52–7.20 (m, 7H), 7.00 (s, 1H), 3.72 (s, 3H), 1.79 (d, *J*=0.9 Hz, 3H), 1.35–1.17 (m, 3H), 1.08 (d, *J*=7.3 Hz, 18H).

**4.2.12. Aryl enone 16d.** To a 25 ml round-bottom flask was added alkynoate **14b** (0.950 g, 2.31 mmol), nitrone **15c** (0.435 g, 2.54 mmol, 1.1 equiv), and toluene (10 ml). The flask was heated at 80 °C overnight. The reaction mixture was concentrated under reduced pressure. To the crude material was added CH<sub>2</sub>Cl<sub>2</sub> (10 ml). The flask was cooled to 0 °C. *m*-CPBA (77%, 1.55 g, 6.93 mmol, 3 equiv) was added and the reaction mixture was stirred for one hour at 0 °C. The reaction mixture was quenched with a saturated aqueous solution of Na<sub>2</sub>SO<sub>3</sub> and extracted three times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were added to a larger solution of saturated aqueous Na<sub>2</sub>SO<sub>3</sub> and extracted three times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (19:1 hexanes:ethyl acetate) to afford aryl dienone **96** (1.12 g, 2.02 mmol, 88% yield) as an inseparable mixture of geometric isomers (1.7:1) and vibrant yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.62 (s, 1H, maj. isomer), 7.49 (s, 1H, maj. isomer), 7.39 (s, 1H, min isomer), 7.29 (s, 1H, maj. isomer), 7.24 (t, *J*=1.9 Hz, 1H, maj. isomer), 7.20 (t, *J*=1.9 Hz, 1H, min isomer), 7.08 (s, 1H, min isomer), 6.86 (s, 1H, min isomer), 6.09 (s, 1H, maj. isomer), 6.02 (s, 1H, min isomer), 3.82 (s, 3H, min isomer), 3.70 (s, 3H, maj. isomer), 1.97 (s, 3H, min isomer), 1.68 (s, 3H, maj. isomer), 1.31–1.19 (m, 3H), 1.15–1.05 (m, 18H), 0.16 (s, 9H, min isomer), 0.08 (s, 9H, maj. isomer); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 193.81, 192.54, 167.28, 165.69, 157.38, 156.93, 150.29, 149.10, 146.88, 146.67, 146.42, 139.92, 139.55, 128.44, 128.31, 127.01, 124.63, 123.31, 122.86, 119.23, 119.12, 52.63, 52.58, 20.01, 18.70,

17.99, 17.95, 17.59, 12.70, –0.39, –0.47; IR (neat, cm<sup>–1</sup>): 2947, 2893, 2866, 1728, 1593, 1562, 1435, 1385, 1366, 1343, 1281, 1250, 1215, 1169, 1099, 1057, 995, 972, 941, 914, 880, 845, 752, 733, 687, 648; HRMS (ESI): Calculated for C<sub>26</sub>H<sub>42</sub>BrO<sub>4</sub>Si<sub>2</sub> ([M+H]<sup>+</sup>): *m/z* 553.1805, found: 552.1814.

**4.2.13. Aryl enone 16e.** To a 50 ml round-bottom flask was added **15d** (0.533 g, 2.5 mmol), **14b** (1.028 g, 2.5 mmol), and toluene (25 ml). The flask was purged with argon for 10 min. The reaction mixture was heated at 80 °C overnight. The solution was concentrated under reduced pressure. To the crude material (1.4 g) was added CH<sub>2</sub>Cl<sub>2</sub> (25 ml). The solution was cooled to 0 °C. *m*-CPBA (77%, 1.00 g) was added, and the solution stirred for 30 min. The reaction was quenched with a saturated aqueous solution of Na<sub>2</sub>SO<sub>3</sub>, diluted and extracted with ether, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (19:1 hexanes:ethyl acetate) to afford **16e** (1.147 g, 77%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.63 (s, 1H), 7.51 (s, 1H), 7.32–7.28 (m, 1H), 7.23 (t, *J*=1.9 Hz, 1H), 6.09 (s, 1H), 3.70 (s, 3H), 1.70 (s, 3H), 1.33–1.17 (m, 3H), 1.08 (d, *J*=7.3 Hz, 18H), 0.83 (s, 9H), 0.03 (s, 6H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 193.74, 165.70, 157.36, 149.29, 147.51, 143.56, 139.41, 128.34, 128.28, 124.66, 123.30, 119.25, 52.66, 26.42, 20.35, 17.94, 17.23, 12.68, –4.65.

**4.2.14. Indanone 17.** In a 10 mL round-bottom flask, Cu(OTf)<sub>2</sub> (51.5 mg, 0.1 mmol) was weighed, and a solution of **13** (467.3 mg, 1.3 mmol) and DCE (5 mL) was added. The reaction was stirred in an oil bath at 60 °C for 1.5 h, then filtered through a plug of silica gel and concentrated, yielding 372.6 mg (81%) of **17**. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.38–7.25 (m, 5H), 6.78 (d, *J*=2.0 Hz, 1H), 6.68 (d, *J*=2.0 Hz, 1H), 6.50 (d, *J*=15.6 Hz, 1H), 6.24 (dd, *J*=8.0, 15.6 Hz, 1H), 4.53 (dd, *J*=2.8, 8.0 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 6H), 3.62 (d, *J*=3.2 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 198.4, 168.7, 161.8, 157.9, 137.3, 137.0, 136.8, 131.1, 128.9, 128.4, 127.4, 126.2, 126.0, 106.6, 96.6, 60.9, 55.6, 52.7, 43.3; IR (neat, cm<sup>–1</sup>): 3003.4, 2950.9, 2941.2, 1738.2, 1708.8, 1611.4, 1493.8, 1306.2, 1203.0; HRMS (EI) calculated for C<sub>21</sub>H<sub>21</sub>O<sub>5</sub> 353.1384, found 353.1369.

**4.2.15. Indanone 18a.** In a dry 10 mL round-bottom flask was weighed Cu(ClO<sub>4</sub>)<sub>2</sub> (7.0 mg, 0.03 mmol), and a solution of **16a** (341 mg, 0.5 mmol) in DCE (5 mL) was added. The solution was stirred at 45 °C and monitored by NMR (aliquots were periodically removed from the reaction, filtered through Celite with CH<sub>2</sub>Cl<sub>2</sub>, and concentrated) for 8 h, then the reaction mixture was filtered through a plug of silica gel and flushed with CH<sub>2</sub>Cl<sub>2</sub> then concentrated. The crude material was purified by column chromatography (10:1 petroleum ether:ether), yielding 272 mg (80%) of **18a**. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.35–7.15 (m, 5H), 6.88 (d, *J*=2.0 Hz, 1H), 6.66 (d, *J*=2.0 Hz, 1H), 6.26 (s, 1H), 4.46 (d, *J*=3.2 Hz, 1H), 3.78 (s, 3H), 3.49 (d, *J*=3.2 Hz, 1H), 1.64 (s, 3H), 1.24 (m, 6H), 1.12 (d, *J*=9.0 Hz, 36H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 198.7, 169.2, 157.7, 154.5, 138.3, 138.2, 137.6, 137.4, 128.8, 127.9, 126.2, 117.3, 106.7, 61.0, 52.8, 50.0, 17.8, 12.5; IR (neat, cm<sup>–1</sup>): 2945.1, 2891.1, 2866.0, 1747.4, 1712.7, 1606.6, 1479.3, 1348.2, 1180.4; HRMS (EI) calculated for C<sub>38</sub>H<sub>58</sub>O<sub>5</sub>Si<sub>2</sub> 650.3817, found 650.3817.

**4.2.16. Indanone 18b.** In a dry 10 mL round-bottom flask was weighed Cu(ClO<sub>4</sub>)<sub>2</sub> (13.0 mg, 0.05 mmol), and a solution of crude **16b** from previous step in DCE (10 mL) was added. The solution was stirred at room temperature and monitored by NMR (aliquots were periodically removed from the reaction, filtered through Celite with CH<sub>2</sub>Cl<sub>2</sub>, and concentrated) for 2 h, then the reaction mixture was filtered through a plug of silica gel and flushed with CH<sub>2</sub>Cl<sub>2</sub> concentrated. The crude material was used for the next step. **18b** was characterized as two isomers (3:1) <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.84

(d, 1H,  $J=2.0$  Hz, maj. isomer), 6.76 (d, 1H,  $J=2.0$  Hz, min isomer), 6.63 (d, 1H,  $J=2.0$  Hz, maj. isomer), 6.42 (d, 1H,  $J=2.0$  Hz, min isomer), 5.15 (s, 1H, min isomer), 4.96 (s, 1H, min isomer), 4.82 (s, 1H, maj. isomer), 4.70 (s, 1H, maj. isomer), 4.34 (s, 1H, min isomer), 4.30 (d, 1H,  $J=2.8$  Hz, maj. isomer), 3.81 (s, 1H, maj. isomer), 3.79 (s, 2.25H), 3.69 (s, 0.25H), 3.41 (d, 0.75H,  $J=3.2$  Hz), 1.63 (s, 3H, maj. isomer), 1.58 (s, 3H, min isomer), 1.31–1.22 (m, 6H, both isomers), 1.13–1.11 (m, 36H, both isomers);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  198.7, 169.3, 157.6, 156.9, 154.4, 153.0, 144.2, 141.4, 138.7, 138.5, 138.0, 117.3, 114.8, 112.6, 112.2, 106.6, 105.9, 105.0, 60.8, 52.7, 51.1, 50.3, 47.9, 29.7, 20.1, 17.9, 17.8, 13.3, 13.1, 12.6; IR (neat) 2945, 2892, 2867, 1720, 1605, 1478, 1348, 1310, 1248, 1176, 882, 766  $\text{cm}^{-1}$ ; HRMS  $m/z$  calcd for  $\text{C}_{32}\text{H}_{54}\text{O}_5\text{NaSi}_2$  ( $\text{M}+\text{Na}^+$ ) 597.3402, found 597.3402.

**4.2.17. Indanone 18c.** To a flame-dried 25 ml round-bottom flask in a glove box was added  $\text{Sc}(\text{OTf})_3$  (0.03 g, 0.06 mmol, 0.05 equiv) and  $\text{Li}(\text{ClO}_4)$  (0.03 g, 0.18 mmol, 0.15 equiv). The flask was removed from the glove box and dry DCE (12 ml) was added. **16c** (0.67 g, 1.2 mmol) was added, and the reaction mixture was heated at 45 °C overnight. The reaction mixture was quenched with water, extracted with ether, dried over  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (9:1 hexane:ethyl acetate) to afford **18c** as a 3:1 mixture of *anti:syn* isomers (0.546 g, 81%). For major (presumably *anti*) isomer:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.39 (d,  $J=2.2$  Hz, 1H), 7.37–7.20 (m, 5H), 7.18 (d,  $J=2.2$  Hz, 1H), 6.38 (s, 1H), 4.47 (d,  $J=3.0$  Hz, 1H), 3.81 (s, 3H), 3.61 (d,  $J=3.0$  Hz, 1H), 1.70 (d,  $J=1.1$  Hz, 3H), 1.35–1.23 (m, 3H), 1.11 (d,  $J=7.2$  Hz, 18H).

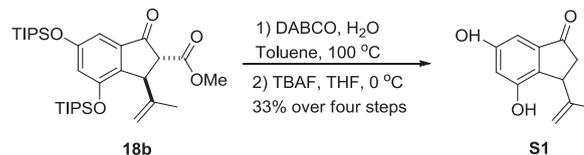
**4.2.18. Indanone 18d.** To a 25 ml round-bottom flask in a glove box was added  $\text{AlCl}_3$  (0.231 g, 1.73 mmol, 1.1 equiv). The flask was removed from the glove box and DCE (15 ml) was added. The flask was cooled to 0 °C. Aryl enone **16d** (0.869 g, 1.57 mmol) was added, and the reaction mixture turned deep red. The reaction mixture was stirred for 30 min. The reaction mixture was quenched with saturated aqueous potassium sodium tartrate, which turned the reaction mixture green, then yellow. The reaction mixture was extracted three times with  $\text{Et}_2\text{O}$ . The combined organic extracts were washed with brine, dried over  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (19:1 hexanes:ethyl acetate) to afford **110** as a 3.6:1 mixture of *anti:syn* isomers (0.597 g, 1.24 mmol, 79% yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37 (d,  $J=2.2$  Hz, 1H, maj. isomer), 7.15 (d,  $J=2.2$  Hz, 1H, maj. isomer), 7.09 (d,  $J=2.2$  Hz, 1H, min isomer), 7.06 (d,  $J=2.2$  Hz, 1H, min isomer), 5.19 (s, 1H, min isomer), 5.09 (s, 1H, min isomer), 4.92 (s, 1H, maj. isomer), 4.69 (s, 1H, maj. isomer), 4.30 (s, 1H, min isomer), 4.28 (d,  $J=2.7$  Hz, 1H, maj. isomer), 3.82 (s, 3H, min isomer), 3.78 (s, 3H, maj. isomer), 3.50 (d,  $J=2.7$  Hz, 1H, maj. isomer), 2.34 (d,  $J=4.5$  Hz, 1H, min isomer), 1.64 (s, 3H), 1.35–1.20 (m, 3H), 1.15–1.05 (m, 18H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  197.82, 168.72, 157.41, 157.30, 156.72, 146.72, 143.52, 139.76, 139.38, 138.48, 131.91, 125.57, 123.67, 122.40, 119.91, 117.07, 114.25, 113.05, 111.15, 107.44, 107.15, 61.23, 53.09, 52.98, 51.46, 50.48, 48.17, 20.53, 18.63, 17.96, 17.59, 17.39, 16.94, 13.00, 12.69. IR (neat,  $\text{cm}^{-1}$ ): 2947, 2866, 1721, 1651, 1586, 1555, 1458, 1377, 1292, 1219, 1157, 1134, 1069, 961, 883, 799, 729, 687, 648; HRMS (ESI): Calculated for  $\text{C}_{23}\text{H}_{34}\text{BrO}_4\text{Si}$  ( $[\text{M}+\text{H}]^+$ ):  $m/z$  481.1410, found: 481.1402.

**4.2.19. Indanone 19.** In a 200 mL round-bottom flask, indanone **18a** (2.6 g, 4.0 mmol) was dissolved in toluene (45 mL), then water (1 mL) and DABCO (224.8 mg, 2.0 mmol) were added. The solution was refluxed for 12 h, and quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (100 mL). The layers were separated and the organic phase was washed with water ( $2 \times 100$  mL) then brine (100 mL). The organic layer was dried over  $\text{MgSO}_4$ , filtered, and concentrated in vacuo.

The crude product was purified by column chromatography (16:1 hexanes:ethyl acetate) to give 2.4 g (99%) of decarboxylated indanone.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.35–7.15 (m, 5H), 6.87 (d,  $J=1.6$  Hz, 1H), 6.63 (d,  $J=2.0$  Hz, 1H), 6.23 (s, 1H), 4.14 (dd,  $J=2.0$ , 8.0 Hz, 1H), 3.02 (dd,  $J=8.0$ , 19.2 Hz, 1H), 2.47 (dd,  $J=2.0$ , 19.2 Hz, 1H), 1.70 (s, 3H), 1.24 (m, 6H), 1.07 (d,  $J=7.4$  Hz, 36H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  206.1, 157.4, 154.6, 140.0, 139.3, 139.1, 138.0, 128.8, 127.9, 126.0, 125.6, 116.5, 105.9, 45.3, 44.6, 17.8, 15.5, 13.0, 12.6; IR (neat,  $\text{cm}^{-1}$ ): 2943.7, 2865.5, 1715.6, 1470.1, 1343.8, 1175.1; HRMS (EI) calculated for  $\text{C}_{36}\text{H}_{57}\text{O}_3\text{Si}_2$  593.3841, found 593.3829.

In a 10 mL round-bottom flask, a solution of *i*- $\text{Pr}_2\text{NH}$  (0.2 mL, 1.0 mmol), *n*- $\text{BuLi}$  (2.5 M solution in hexanes, 0.3 mL, 0.7 mmol), and THF (1 mL) was stirred at 0 °C for 15 min, then cooled to –40 °C. A solution of the decarboxylated material (300.0 mg, 0.5 mmol) in THF (2 mL) was added, and the reaction was stirred at –40 °C for 5.5 h, then  $\text{MeI}$  (0.2 mL, 3.2 mmol) was added and the reaction was stirred for an additional 4 h at –20 °C. The reaction was quenched while cold with saturated aqueous  $\text{NH}_4\text{Cl}$  and the layers were separated. The organic phase was diluted with hexanes (10 mL) and washed with water ( $3 \times 10$  mL), then brine (10 mL). The organic layer was dried over  $\text{MgSO}_4$ , filtered, and concentrated in vacuo. The crude product was purified by column chromatography (16:1 hexanes:ethyl acetate) to give 247.3 mg (81%) of **19**.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.35–7.15 (m, 5H), 6.87 (d,  $J=2.0$  Hz, 1H), 6.62 (d,  $J=2.0$  Hz, 1H), 6.30 (s, 1H), 3.60 (d,  $J=3.2$  Hz, 1H), 2.43 (dt,  $J=7.4$ , 3.2 Hz, 1H), 1.72 (s, 3H), 1.36 (d,  $J=7.4$  Hz, 3H), 1.24 (m, 6H), 1.07 (d,  $J=7.4$  Hz, 36H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  208.6, 157.4, 154.7, 139.1, 138.7, 138.0, 137.6, 128.9, 127.9, 126.0, 125.7, 116.6, 106.2, 55.1, 49.9, 17.8, 15.9, 15.2, 13.1, 12.6; IR (neat,  $\text{cm}^{-1}$ ): 2943.2, 2866.0, 1715.6, 1604.7, 1470.6, 1341.9, 1174.6; HRMS (EI) calculated for  $\text{C}_{37}\text{H}_{59}\text{O}_3\text{Si}_2$  607.3997, found 607.3998.



**4.2.20. Indanone 51.** In a 200 mL round-bottom flask, crude **18b** (207 mg, 0.36 mmol) from previous steps was dissolved in toluene (4.1 mL), then water (0.41 mL) and DABCO (21 mg, 0.18 mmol) were added. The solution was refluxed for 12 h, and quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (100 mL). The layers were separated and the organic phase was washed with water ( $2 \times 100$  mL) then brine (100 mL). The organic layer was dried over  $\text{MgSO}_4$ , filtered, and concentrated in vacuo. The crude material was used for the next step.

In a 25 mL round-bottom flask, the crude material from previous step was dissolved in THF (3.1 mL) and the solution was cooled to 0 °C, then TBAF (1.0 M solution in THF, 0.6 mL, 0.6 mmol) was added and the reaction was stirred for 1 h. The solution was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  and the layers were separated. The organic phase was diluted with diethyl ether (20 mL) and washed with water ( $3 \times 10$  mL), then brine (10 mL). The organic layer was dried over  $\text{MgSO}_4$ , filtered, and concentrated in vacuo. The crude product was purified by column chromatography (1:1 hexanes:ethyl acetate) to give 66 mg (33%, yield over 4 steps from **14a**) of **51**.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  6.59 (d, 1H,  $J=2.0$  Hz), 5.56 (d, 1H,  $J=2.4$  Hz), 4.76 (s, 1H), 4.69 (s, 1H), 4.02 (dd, 1H,  $J=2.0$ , 7.6 Hz), 2.94 (dd, 1H,  $J=8.0$ , 19.2 Hz), 2.34 (dd, 1H,  $J=2.0$ , 19.2 Hz), 1.60 (s, 3H).

**4.2.21. Aryl triflate 20.** In a 25 mL round-bottom flask, diprotected **19** (402.0 mg, 0.7 mmol) was dissolved in THF (6 mL) and the solution was cooled to 0 °C, then TBAF (1.0 M solution in THF, 1.2 mL,

1.2 mmol) was added and the reaction was stirred for 1 h. The solution was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  and the layers were separated. The organic phase was diluted with diethyl ether (20 mL) and washed with water ( $3 \times 10$  mL), then brine (10 mL). The organic layer was dried over  $\text{MgSO}_4$ , filtered, and concentrated in vacuo. The crude product was purified by column chromatography (2:1 hexanes:ethyl acetate) to give 147.4 mg (76%) of diphenol.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.38–7.30 (m, 5H), 6.93 (d,  $J=2.0$  Hz, 1H), 6.72 (d,  $J=2.0$  Hz, 1H), 6.71 (s, 1H), 3.67 (d,  $J=4.0$  Hz, 1H), 2.60 (dt,  $J=7.2, 4.0$  Hz, 1H), 1.76 (s, 3H), 1.37 (d,  $J=7.2$  Hz, 3H).

In a 25 mL round-bottom flask, diol from the previous step (240.0 mg, 0.8 mmol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (11 mL), and TEA (0.1 mL, 0.7 mmol) and TIPS-Cl (0.2 mL, 0.8 mmol) were added. The reaction was stirred for 16 h, then quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  and the layers were separated. The organic phase was diluted with  $\text{CH}_2\text{Cl}_2$  (10 mL) and washed with water (10 mL), then brine (10 mL). The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated in vacuo. The crude product was purified by column chromatography (15:1 hexanes:ethyl acetate) to give 155.6 mg (42%) of monophenol.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.38–7.30 (m, 5H), 6.86 (d,  $J=2.0$  Hz, 1H), 6.75 (s, 1H), 6.68 (d,  $J=2.0$  Hz, 1H), 5.68 (s, 1H), 3.68 (d,  $J=4.4$  Hz, 1H), 2.57 (dt,  $J=7.2, 4.4$  Hz, 1H), 1.78 (s, 3H), 1.37 (d,  $J=7.2$  Hz, 3H), 1.28 (m, 3H), 1.09 (d,  $J=7.4$  Hz, 18H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  207.4, 158.1, 154.8, 138.6, 138.1, 136.7, 131.8, 128.9, 128.3, 128.2, 127.1, 114.0, 106.3, 55.0, 48.6, 17.7, 14.7, 14.2, 12.6; IR (neat,  $\text{cm}^{-1}$ ): 3204.8, 2943.2, 2865.5, 1680.9, 1470.1, 1345.7, 1177.5; HRMS (EI) calculated for  $\text{C}_{28}\text{H}_{39}\text{O}_3\text{Si}$  451.2663, found 451.2648.

In a 25 mL round-bottom flask, monophenol from the previous step (155.6 mg, 0.4 mmol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (2 mL) and cooled to  $0^\circ\text{C}$ , then pyridine (0.08 mL, 1.0 mmol) and  $\text{Tf}_2\text{O}$  (0.1 mL, 0.6 mmol) were added and the reaction was stirred in an ice bath for 2 h. The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  and the layers were separated. The organic phase was diluted with hexanes (15 mL) and washed with brine (10 mL). The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated in vacuo. The crude product was purified by column chromatography (8:1 hexanes:ethyl acetate) to give 190.2 mg (93%) of aryl triflate **20**.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.38–7.30 (m, 6H), 7.05 (d,  $J=2.4$  Hz, 1H), 6.56 (s, 1H), 3.83 (d,  $J=4.0$  Hz, 1H), 2.58 (dt,  $J=7.2, 4.0$  Hz, 1H), 1.67 (s, 3H), 1.40 (d,  $J=7.2$  Hz, 3H), 1.27 (m, 3H), 1.12 (d,  $J=7.2$  Hz, 18H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  205.8, 157.7, 147.3, 140.3, 138.0, 137.4, 134.9, 129.1, 128.9, 128.8, 128.0, 126.5, 119.9, 113.9, 55.0, 50.9, 49.1, 17.7, 14.8, 14.2, 12.5; IR (neat,  $\text{cm}^{-1}$ ): 2944.6, 2868.0, 1723.8, 1615.3, 1470.6, 1424.3, 1313.4, 1245.0, 1207.8, 1139.0, 992.3; HRMS (EI) calculated for  $\text{C}_{29}\text{H}_{37}\text{O}_5\text{SiF}_3$  582.2078, found 582.2077.

**4.2.22. Aryl triflate 21.** **21** was prepared following the synthetic procedure for **20**, except methylation was not carried out.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.36–7.32 (t,  $J=7.2$  Hz, 2H), 7.28–7.23 (m, 3H), 7.07 (d,  $J=2.4$  Hz, 1H), 6.53 (s, 1H), 4.39 (dd,  $J=2.8, 8.0$  Hz, 1H), 3.10 (dd,  $J=8.4, 19.6$  Hz, 1H), 2.63 (dd,  $J=3.2, 19.6$  Hz, 1H), 1.62 (s, 3H), 1.32–1.27 (m, 3H), 1.13–1.11 (m, 18H);  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  203.7, 157.8, 147.3, 141.1, 139.7, 137.3, 135.7, 128.9, 128.5, 128.1, 126.6, 120.0, 113.7, 53.4, 45.5, 43.5, 17.7, 14.1, 12.5; IR (neat) 2946, 2868, 1725, 1617, 1476, 1426, 1315, 1245, 1217, 1141, 1064, 999, 942, 882  $\text{cm}^{-1}$ ; HRMS  $m/z$  calcd for  $\text{C}_{28}\text{H}_{35}\text{O}_5\text{F}_3\text{NaSSi}$  ( $\text{M}+\text{Na}^+$ ) 591.1819, found 591.1824.

**4.2.23. Aryl triflate 22.** In a 25 mL round-bottom flask, **21** (569 mg, 1 mmol) was dissolved in THF (8.6 mL) and the solution was cooled to  $0^\circ\text{C}$ , then TBAF (1.0 M solution in THF, 1.7 mL, 1.7 mmol) was added and the reaction was stirred for 1 h. The solution was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  and the layers were separated. The organic phase was diluted with diethyl ether (20 mL) and washed with water ( $3 \times 10$  mL), then brine (10 mL).

The organic layer was dried over  $\text{MgSO}_4$ , filtered, and concentrated in vacuo. The crude product was purified by column chromatography (3:1 hexanes:ethyl acetate) to give 408 mg (99%) of phenol.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.36–7.32 (m, 3H), 7.27–7.22 (m, 3H), 7.12 (m, 1H), 6.53 (s, 1H), 6.34 (b, 1H), 4.40 (dd, 1H,  $J=2.8, 8.0$  Hz), 3.13 (dd, 1H,  $J=8.0, 19.6$  Hz), 2.66 (dd, 1H,  $J=2.8, 19.6$  Hz), 1.63 (s, 3H);  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  204.4, 157.5, 147.6, 141.1, 139.6, 137.2, 135.4, 128.8, 128.6, 128.1, 126.6, 116.3, 109.4, 77.2, 45.5, 43.5, 14.2.

$\text{TMSCHN}_2$  (2.0 M in  $\text{Et}_2\text{O}$ , 0.275 mL, 0.55 mmol) was added to a stirred solution of phenol from the previous step (206 mg, 0.5 mmol) and *N,N*-diisopropylethylamine (91 mg, 0.7 mmol) in methanol–acetonitrile (1:9, 2 mL) at room temperature. The mixture was stirred for 15 h at room temperature, and concentrated in vacuo. The crude was dissolved in  $\text{Et}_2\text{O}$  (15 mL), washed with saturated aqueous  $\text{NH}_4\text{Cl}$  ( $3 \times 10$  mL) and water ( $3 \times 10$  mL), then brine (10 mL). The organic layer was dried over  $\text{MgSO}_4$ , filtered, and concentrated in vacuo. The crude product was purified by column chromatography (3:1 hexanes:ethyl acetate) to give 186 mg (82%) of **22**.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.36–7.21 (m, 5H), 7.11 (s, 1H), 6.53 (s, 1H), 4.40 (dd,  $J=2.8, 8.0$  Hz, 1H), 3.91 (s, 3H), 3.12 (dd,  $J=8.0, 19.6$  Hz, 1H), 2.65 (dd,  $J=2.8, 19.6$  Hz, 1H), 1.63 (s, 3H);  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  203.7, 161.2, 147.5, 141.3, 139.7, 137.3, 135.7, 128.9, 128.6, 128.1, 126.6, 116.4, 105.8, 77.2, 56.3, 45.5, 43.5, 14.2; IR (neat) 2917, 1720, 1486, 1425, 1296, 1244, 1212, 1140, 1071, 1036, 964, 861  $\text{cm}^{-1}$ ; HRMS  $m/z$  calcd for  $\text{C}_{20}\text{H}_{17}\text{O}_5\text{F}_3\text{S}$  ( $\text{M}^+$ ) 426.0743, found 426.0743.

**4.2.24. Aryl bromide 23.** To a 25 mL round-bottom flask was added DABCO (0.142 g, 1.26 mmol, 1.43 equiv), toluene (8 mL),  $\text{H}_2\text{O}$  (0.8 mL), and **18c** (0.491 g, 0.882 mmol). The flask was purged with argon for 10 min. The reaction mixture was refluxed overnight. The reaction mixture was diluted with water and ether, extracted with ether, dried over  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (19:1 ether:hexane) to afford aryl bromide **23** (0.371 g, 84%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.37 (d,  $J=2.2$  Hz, 1H), 7.34–7.20 (m, 5H), 7.19 (d,  $J=2.2$  Hz, 1H), 6.39 (s, 1H), 4.15 (dd,  $J=8.0, 2.0$  Hz, 1H), 3.08 (dd,  $J=19.3, 8.0$  Hz, 1H), 2.61 (dd,  $J=19.3, 2.0$  Hz, 1H), 1.63 (s, 3H), 1.40–1.20 (m, 3H), 1.11 (d,  $J=7.3$  Hz, 18H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  204.98, 157.16, 147.42, 140.36, 137.89, 137.30, 131.25, 128.86, 128.23, 126.52, 122.57, 112.37, 44.44, 18.02, 17.89, 12.72.

**4.2.25. Alcohol 24.** To a 25 mL round-bottom flask was added **18d** (0.475 g, 0.987 mmol), DABCO (0.055 g, 0.493 mmol, 0.5 equiv), toluene (10 mL), and  $\text{H}_2\text{O}$  (1 mL). The solution was heated at  $80^\circ\text{C}$  overnight. The solution was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  and extracted three times with  $\text{Et}_2\text{O}$ . The combined organic extracts were washed with brine, dried over  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (19:1 hexanes:ethyl acetate) to afford decarboxylated indanone (0.382 g, 0.902 mmol 91% yield).

LDA was prepared according to the following: to a 50 mL round-bottom flask was added THF (15 mL) and diisopropylamine (1.37 mL, 9.74 mmol, 1.21 equiv). The solution was cooled to  $-40^\circ\text{C}$ , and *n*-BuLi (3.66 mL, 2.42M in hexanes, 1.1 equiv) was added. The solution was stirred at  $-40^\circ\text{C}$  for 40 min. Then, decarboxylated indanone from the previous step (3.41 g, 8.05 mmol), in THF (38 mL) was added dropwise. The solution was stirred and maintained at  $-40^\circ\text{C}$  for three hours. Then, MeI (24.9 mL, 400 mmol, 50 equiv) was added to the solution, which was slowly raised to room temperature overnight. The reaction was quenched the next day with 1M aqueous HCl and extracted three times with  $\text{Et}_2\text{O}$ . The combined organic fractions were washed with saturated  $\text{NaHCO}_3$ , concentrated under reduced pressure, and taken to the next step without further purification.

The crude material from the previous step was dissolved in MeOH (80 ml) and cooled to 0 °C. NaBH<sub>4</sub> (0.610 g, 16.1 mmol, 2 equiv) was added. The reaction was stirred at 0 °C for 2 h, then quenched with water. The solution was extracted three times with Et<sub>2</sub>O, and the combined organic extracts were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (19:1 hexanes:ethyl acetate) to afford alcohol **24** (2.37 g, 5.39 mmol, 67% over two steps) as a crystalline solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.99 (s, 1H), 6.88 (s, 1H), 4.86 (s, 1H), 4.62 (s, 1H), 4.55 (dd, *J*=8.5, 4.9 Hz, 1H), 3.19 (d, *J*=5.4 Hz, 1H), 2.18 (d, *J*=8.5 Hz, 1H), 2.14–2.07 (m, 1H), 1.74 (s, 3H), 1.30–1.21 (m, 3H), 1.16 (d, *J*=6.9 Hz, 3H), 1.10 (d, *J*=7.4 Hz, 18H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 156.59, 147.61, 147.12, 134.96, 124.24, 120.96, 115.16, 112.45, 82.41, 58.76, 49.23, 20.49, 17.99, 17.89, 12.70. IR (neat, cm<sup>-1</sup>): 3287 (br), 3075 (w), 2943 (s), 2866 (s), 1605 (s), 1555 (s), 1458 (s), 1412 (w), 1377 (w), 1285 (s), 1211 (m), 1177 (m), 1142 (s), 1057 (s), 999 (s), 880 (s), 845 (s), 814 (w), 760 (s), 733 (m), 683 (s), 644 (w); HRMS (ESI): Calculated for C<sub>22</sub>H<sub>35</sub>BrO<sub>2</sub>SiNa ([M+H+Na]<sup>+</sup>): *m/z* 461.1487, found: 461.1492.

**4.2.26. Aryl bromide 25.** To a 100 ml round-bottom flask was added alcohol **24** (2.54 g, 5.78 mmol), TBSCl (3.48 g, 23.1 mmol, 4 equiv), imidazole (3.15 g, 46.2 mmol, 8 equiv), and THF (57 ml). The solution was stirred at room temperature overnight. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl and extracted three times with Et<sub>2</sub>O. The combined organic fractions were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (19:1 hexanes:ethyl acetate) to afford aryl bromide **25** (2.90 g, 5.24 mmol, 91% yield) as a translucent oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.94 (d, *J*=2.2 Hz, 1H), 6.74 (d, *J*=2.2 Hz, 1H), 4.88 (s, 1H), 4.86 (s, 1H), 4.58 (d, *J*=6.3 Hz, 1H), 3.20 (d, *J*=7.2 Hz, 1H), 2.08–1.97 (m, 1H), 1.62 (s, 3H), 1.31–1.19 (m, 3H), 1.15 (d, *J*=6.9 Hz, 3H), 1.09 (d, *J*=7.2 Hz, 18H), 0.93 (s, 9H), 0.17 (s, 3H), 0.14 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 156.27, 148.76, 145.74, 134.25, 123.99, 120.63, 114.67, 113.31, 82.12, 58.89, 49.43, 25.92, 19.39, 18.13, 18.03, 17.25, 12.78, -3.95, -4.12. IR (neat, cm<sup>-1</sup>): 2951, 2931, 2893, 2866, 1605, 1559, 1458, 1362, 1296, 1254, 1180, 1146, 1115, 1067, 999, 868, 833, 772, 733, 683, 671.

**4.2.27. Amine 28.** An oven-dried resealable Schlenk flask was evacuated and backfilled with argon. The flask was charged with Pd(OAc)<sub>2</sub> (10 mol %), BINAP (20 mol %), and NaO<sup>t</sup>Bu (1.4 equiv) and evacuated and backfilled with argon. The flask was capped with a rubber septum, and toluene (2 mL/mmol triflate), the aryl triflate **21** (57 mg, 0.1 mmol, 1.0 equiv), and the amine **27** (1.2 equiv) were added through the septum. The septum was replaced with a Teflon screwcap, the flask was sealed, and the mixture was heated to 105 °C with stirring. The mixture was cooled to room temperature, diluted with ether, filtered through Celite, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to furnish amine **28** (3 mg, 6%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.36–7.20 (m, 5H), 6.83 (s, 1H), 6.65 (s, 1H), 6.36 (s, 1H), 4.16 (dd, *J*=2.0, 8.0 Hz, 1H), 3.82 (s, 3H), 3.00 (dd, *J*=8.0, 19.0 Hz, 1H), 2.53 (dd, *J*=2.0, 19.0 Hz, 1H), 1.64 (s, 3H), 1.32–1.28 (m, 3H), 1.26 (s, 6H), 1.13–1.11 (m, 18H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ 206.1, 158.2, 157.8, 139.7, 138.6, 138.2, 137.9, 128.8, 128.2, 128.0, 126.12, 126.09, 109.5, 104.4, 55.6, 45.2, 43.9, 29.7, 22.7, 17.9, 14.8, 12.7; IR (neat, cm<sup>-1</sup>) 2925, 2866, 1718, 1608, 1480, 1445, 1344, 1308, 1220, 1196, 1167, 992, 883.

**4.2.28. Amine 30.** An oven-dried resealable Schlenk flask was evacuated and backfilled with argon. The flask was charged with Pd<sub>2</sub>(dba)<sub>3</sub> (5 mol %), DavePhos (10 mol %), and K<sub>3</sub>PO<sub>4</sub> (1.4 equiv) and evacuated and backfilled with argon. The flask was capped with a rubber septum, and toluene (2 mL/mmol triflate), the aryl triflate **22** (18 mg, 0.04 mmol, 1.0 equiv), and the amine **29** (1.2 equiv) were added through the septum. The septum was replaced with a Teflon

screwcap, the flask was sealed, and the mixture was heated to 105 °C with stirring. The mixture was cooled to room temperature, diluted with ether, filtered through Celite, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to furnish amine **30** as a 3:1 mixture of isomers (6 mg, 40%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.36–7.24 (m, 5H, both isomers), 6.76 (s, 1H, both isomers), 6.66 (d, *J*=2.4 Hz, 1H, both isomers), 6.26 (d, *J*=2.0 Hz, 1H, both isomers), 4.93 (d, *J*=8.8 Hz, 1H, maj. isomer), 4.77 (d, *J*=8.0 Hz, 1H, min isomer), 4.15–4.08 (m, 2H, both isomers), 3.82 (s, 3H, both isomers), 3.75 (s, 3H, min isomer), 3.66 (s, 3H, maj. isomer), 3.03 (dd, *J*=8.0, 19.2 Hz, 1H, both isomers), 2.57 (dd, *J*=2.8, 19.2 Hz, 1H, both isomers), 1.67 (s, 3H, maj. isomer) 1.63 (s, 3H, min isomer) 1.43 (d, *J*=6.8 Hz, 3H, maj. isomer) 1.41 (d, *J*=7.2 Hz, 3H, min. isomer); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ 205.9, 174.2, 161.7, 145.9, 139.5, 138.9, 137.3, 135.2, 128.8, 128.7, 128.4, 128.2, 128.1, 126.7, 103.9, 103.8, 93.7, 93.6, 55.5, 52.4, 52.2, 51.5, 51.2, 46.2, 43.1, 29.7, 18.7, 18.6, 13.5, 13.4; IR (neat) 2923, 1743, 1707, 1612, 1514, 1449, 1363, 1204, 1170, 1087, 1049 cm<sup>-1</sup>; HRMS *m/z* calcd for C<sub>23</sub>H<sub>25</sub>O<sub>4</sub>NNa (M+Na<sup>+</sup>) 402.1676, found 402.1668.

**4.2.29. Amine 32.** An oven-dried resealable Schlenk flask was evacuated and backfilled with argon. The flask was charged with Pd(OAc)<sub>2</sub> (10 mol %), BINAP (15 mol %), and Cs<sub>2</sub>CO<sub>3</sub> (1.4 equiv) and evacuated and backfilled with argon. The flask was capped with a rubber septum, and toluene (2 mL/mmol triflate), the aryl triflate **22** (18 mg, 0.04 mmol, 1.0 equiv), and the amine **31** (1.2 equiv) were added through the septum. The septum was replaced with a Teflon screwcap, the flask was sealed, and the mixture was heated to 100 °C with stirring. The mixture was cooled to room temperature, diluted with ether, filtered through Celite, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to furnish amine **32** (8 mg, 50%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.32–7.23 (m, 8H), 7.10 (m, 2H), 6.64 (d, *J*=1.5 Hz, 1H), 6.61 (s, 1H), 6.39 (d, *J*=1.5 Hz, 1H), 4.67 (s, 1H), 4.32 (d, *J*=5.0 Hz, 2H), 4.08 (dd, *J*=2.0, 7.5 Hz, 1H), 3.82 (s, 3H), 3.03 (dd, *J*=7.5, 19.0 Hz, 1H), 2.57 (dd, *J*=2.5, 19.0 Hz, 1H), 1.64 (s, 3H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ 206.0, 161.8, 147.0, 139.3, 138.8, 138.3, 137.0, 134.7, 128.8, 128.7, 128.2, 128.0, 127.5, 127.4, 126.7, 103.6, 93.0, 55.5, 47.9, 46.4, 43.2, 13.6; IR (neat) 2921, 2851, 1703, 1610, 1511, 1451, 1365, 1237, 1202, 1166, 1061 cm<sup>-1</sup>; HRMS *m/z* calcd for C<sub>26</sub>H<sub>25</sub>O<sub>2</sub>N (M<sup>+</sup>) 383.1880, found 383.1885.

**4.2.30. Amine 34.** An oven-dried resealable Schlenk flask was evacuated and backfilled with argon. The flask was charged with Pd<sub>2</sub>(dba)<sub>3</sub> (3 mol %), BINAP (4.5 mol %), and NaO<sup>t</sup>Bu (1.4 equiv) and evacuated and backfilled with argon. The flask was capped with a rubber septum, and toluene (2 mL/mmol triflate), the aryl triflate **21** (69 mg, 0.121 mmol, 1.0 equiv), and the amine **33** (1.2 equiv) were added through the septum. The septum was replaced with a Teflon screwcap, the flask was sealed, and the mixture was heated to 90 °C with stirring. The mixture was cooled to room temperature, diluted with ether, filtered through Celite, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to furnish amine **34** (20 mg, 28%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.70 (d, *J*=7.2 Hz, 2H), 7.50–7.45 (m, 1H), 7.32–7.21 (m, 7H), 7.19–7.16 (m, 1H), 7.12–7.05 (m, 2H), 7.08–7.01 (m, 2H), 6.89 (s, 1H), 6.43–6.48 (m, 1H), 6.36 (s, 1H), 3.89 (dd, *J*=2.8, 8.0 Hz, 1H), 2.87 (dd, *J*=8.0, 19.2 Hz, 1H), 2.52 (dd, *J*=2.8, 19.2 Hz, 1H), 1.64 (s, 3H), 1.14–1.07 (m, 3H), 1.03–1.01 (m, 18H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ 206.1, 167.7, 156.5, 149.8, 139.5, 139.2, 138.8, 137.7, 135.8, 130.9, 129.6, 129.0, 128.9, 128.8, 128.1, 127.8, 127.4, 126.0, 118.5, 108.3, 77.2, 46.6, 43.6, 17.8, 13.9, 12.4; IR (neat) 2942, 2865, 1713, 1661, 1598, 1465, 1447, 1317, 1278, 1178, 1072, 1000, 941, 919, 883 cm<sup>-1</sup>; HRMS *m/z* calcd for C<sub>40</sub>H<sub>46</sub>O<sub>2</sub>NSi (M+H<sup>+</sup>) 600.3292, found 600.3306.

**4.2.31. Amine 35.** To a flame-dried 3 ml vial in a glove box was added Pd<sub>2</sub>(dba)<sub>3</sub> (0.0046 g, 0.005 mmol, 0.05 equiv), BINAP

(0.011 g, 0.015 mmol, 0.15 equiv), and NaO<sup>t</sup>Bu (0.0115 g, 0.12 mmol, 1.2 equiv). The vial was capped with a pierceable PFTE seal. The vial was removed from the glove box and dry toluene (0.6 ml) was added. The mixture was stirred for five minutes. **33** (0.025 ml, 0.15 mmol, 1.5 equiv) and **23** (0.050 g, 0.1 mmol) were added by syringe, and the vial was heated at 110 °C behind a blast shield overnight. The reaction mixture was concentrated under reduced pressure. The crude residue was dissolved in THF (0.33 ml) in a 5 ml round-bottom flask. 1M aqueous HCl was added (0.033 ml) and the reaction was stirred for 15 min. The reaction was quenched with aqueous saturated NaHCO<sub>3</sub>, diluted and extracted with ether, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (9:1 hexane:ethyl acetate) to afford aniline **35** (11.6 mg, 27%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.41–7.13 (m, 5H), 6.69 (d, *J*=2.0 Hz, 1H), 6.64 (s, 1H), 6.45 (d, *J*=2.0 Hz, 1H), 4.07 (dd, *J*=7.8, 2.6 Hz, 1H), 3.99 (s, 2H), 3.01 (dd, *J*=19.3, 7.8 Hz, 1H), 2.53 (dd, *J*=19.3, 2.6 Hz, 1H), 1.67 (d, *J*=0.9 Hz, 3H), 1.36–1.18 (m, 3H), 1.10 (d, *J*=7.2 Hz, 18H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 206.09, 157.66, 145.81, 139.68, 138.78, 137.29, 133.96, 128.90, 128.39, 127.69, 127.49, 126.84, 103.48, 103.28, 43.46, 18.09, 17.96, 12.75. IR (neat, cm<sup>-1</sup>) 2943, 2865, 1701, 1619, 1482, 1351, 1236, 1184, 1068, 1013, 946, 883; HRMS *m/z* calcd for C<sub>27</sub>H<sub>38</sub>NO<sub>2</sub>Si (M+H<sup>+</sup>) 436.2666, found 436.2658.

**4.2.32. Amine 36.** To a 100 ml Schlenk bomb was added [Pd(allyl)Cl]<sub>2</sub> (0.0192 g, 0.0524 mmol, 0.01 equiv), Mor-DalPhos (0.0974 g, 0.210 mmol, 0.04 equiv), NaO<sup>t</sup>Bu (1.01 g, 10.5 mmol, 2 equiv), and toluene (52 ml). The solution was stirred for 10 min. Then, **25** (2.9 g, 5.24 mmol) was added, followed by NH<sub>3</sub> (0.5 M solution in 1,4-dioxane, 31.4 ml, 3 equiv). The Schlenk bomb was sealed and heated at 110 °C for 1 h. The reaction vessel was cooled, quenched with saturated aqueous NH<sub>4</sub>Cl, and extracted three times with Et<sub>2</sub>O. The combined extracts were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (19:1 hexanes:ethyl acetate) to afford aniline **36** (2.48 g, 5.06 mmol, 97% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.24 (d, *J*=2.0 Hz, 1H), 6.05 (d, *J*=2.0 Hz, 1H), 5.05 (d, *J*=2.0 Hz, 1H), 4.94 (s, 1H), 4.56 (d, *J*=7.4 Hz, 1H), 3.75 (s, 2H), 3.15 (d, *J*=8.4 Hz, 1H), 2.10–1.98 (m, 1H), 1.64 (s, 3H), 1.32–1.16 (m, 3H), 1.14 (d, *J*=6.8 Hz, 3H), 1.09 (d, *J*=7.0 Hz, 18H), 0.95 (s, 9H), 0.17 (s, 3H), 0.14 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 156.72, 147.94, 147.28, 144.22, 118.61, 113.66, 106.24, 105.50, 82.18, 56.32, 49.05, 26.01, 18.26, 18.20, 18.12, 16.32, 12.86, -3.91, -4.00; IR (neat, cm<sup>-1</sup>): 2951, 2928, 2893, 2866, 1613, 1470, 1362, 1254, 1204, 1157, 1096, 1009, 837, 683; HRMS (ESI): Calculated for C<sub>28</sub>H<sub>52</sub>NO<sub>2</sub>Si<sub>2</sub> ([M+H]<sup>+</sup>): *m/z* 490.3537, found: 490.3531.

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## Supplementary data

Supplementary data (<sup>1</sup>H and <sup>13</sup>C NMR spectra for compounds.) related to this article can be found at <http://dx.doi.org/10.1016/j.tet.2015.05.021>.

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