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Note

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Development of Asymmetric Deacylative Allylation

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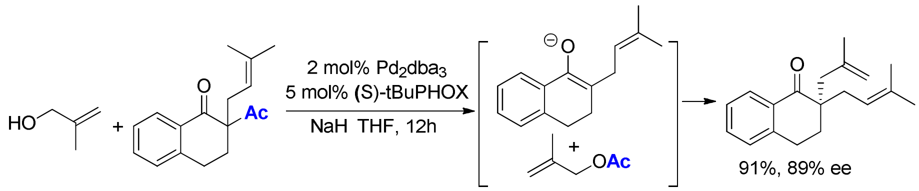
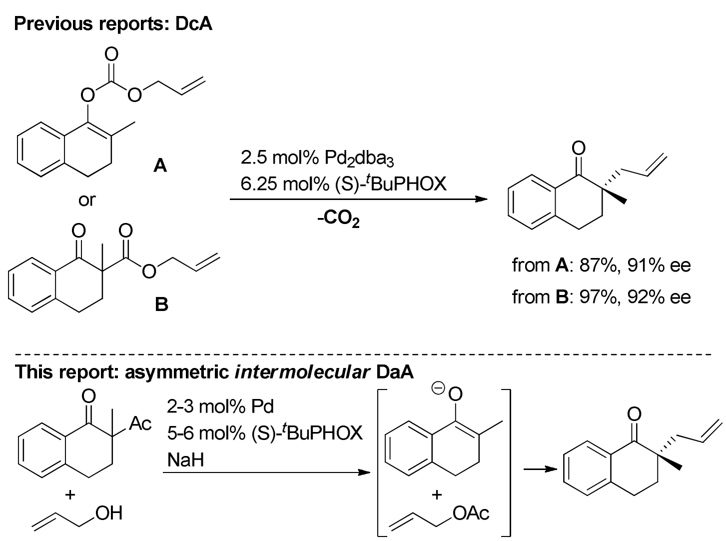


Abstract:

Herein we present the development of asymmetric deacylative allylation of ketone enolates. The reaction directly couples readily available ketone pronucleophiles with allylic alcohols using facile retro-Claisen cleavage to form reactive intermediates *in situ*. The simplicity and robustness of the reaction conditions is demonstrated by the preparation of > 6 grams of an allylated tetralone from commercially available materials. Furthermore, use of non-racemic PHOX ligands allows intermolecular formation of quaternary stereocenters directly from allylic alcohols.

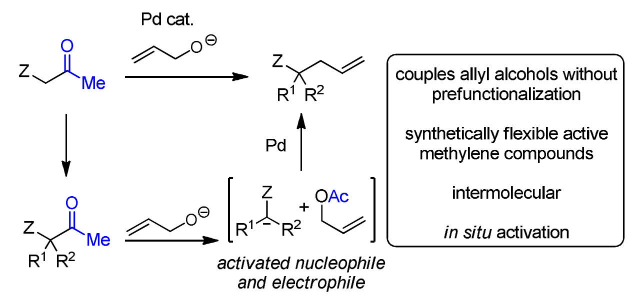
The asymmetric allylation of ketone enolates to form α-quaternary ketones has recently garnered significant attention from the synthetic community.[1-12] The synthetic flexibility of the product ketones has led to the use of these methods in complex molecule synthesis.[10,13-17] The most commonly utilized method for preparing α-quaternary α-allylated ketones is Pd-catalyzed asymmetric allylic alkylation (AAA). First, Trost reported the AAA of nonstabilized ketone enolates (pK_a > 24) involving the allylation of tetralones with allylic acetates in the presence of LDA with or without Me_3SnCl.[3-5] More recently, asymmetric decarboxylative allylation (DcA) methods were reported, which allowed similar allylation in the absence of base and other additives (Scheme 1).[6-17] Although DcA is an attractive advancement, the required substrates **A** and **B** necessitate coupling of the allyl electrophile with the enolate nucleophiles prior to DcA. This process is not ideal because it requires one to control O vs. C alkylation using allyl chloroformate derivatives that are not readily available with a variety of substitution patterns.

Scheme 1: Asymmetric allylic alkylation (AAA) of tetralones



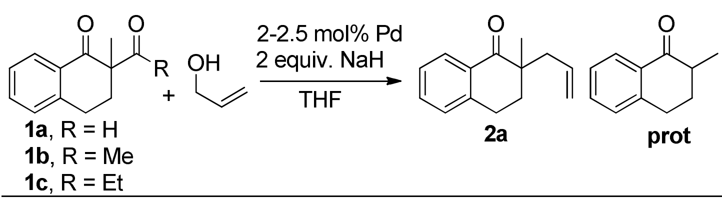
Recently, we have developed deacylative allylation (DaA) as a robust approach to the synthesis of allylated chemical building blocks (Scheme 2).[18,19] This *intermolecular* coupling allows the direct allylation of ketone pronucleophiles (derived from simple active methylene compounds **C**) with readily available allylic alcohols,[20-26] and generates little waste product. DaA takes advantage of the facile retro-Claisen reaction of α,α-disubstituted active methylene compounds to generate enolates and allylic acetates *in situ.*[27-31] In other words, retro-Claisen cleavage results in the formation of the active nucleophile and simultaneously activates the electrophile toward palladium-catalyzed coupling. One example of its utility, we have previously demonstrated DaA's ability to construct 1,6-dienes (cycloisomerization substrates[32-39]) in a single pot via sequential palladium-catalysis.[18-19,40]

Scheme 2: Deacylative allylation (DaA)



Herein, we report the use of the DaA concept for the asymmetric allylic alkylation of nonstabilized ketone enolates. To demonstrate the scalability of DaA, we report a > 6 gram scale reaction. In addition, we report the asymmetric synthesis of various 1,6-heptadienes (72-95% ee) as well as the synthesis of an intermediate *en route* to the biologically active natural product (+)-hamigeran.[14,41] We also outline an approach to either enantiomer of chiral 1,6-heptadienes using *the same chiral catalyst.*

Table 1. DaA: Various cleaving groups and catalysts



Entry	Substrate	Catalyst	**2a** : **prot** (Yield **2a**)
1	**1a**	2.5 mol% $Pd(PPh_3)_4$	75 : 25 (75%)
2	**1a**	2 mol% Pd/rac-BINAP	89 : 11 (83%)
3	**1b**	2.5 mol% $Pd(PPh_3)_4$	95 : 5 (90%)
4	**1c**	2.5 mol% $Pd(PPh_3)_4$	95 : 5 (95%)

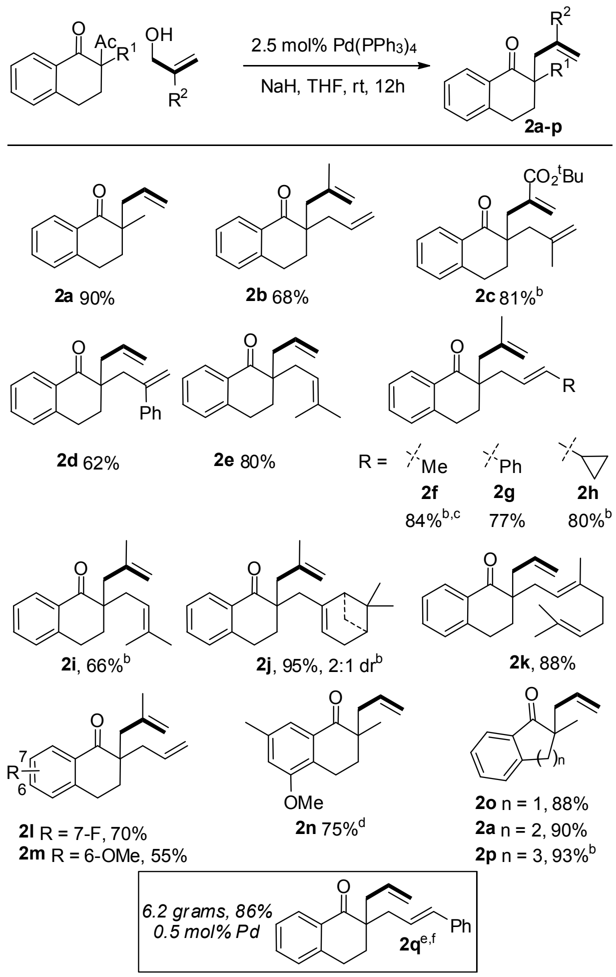
[a] Scale: 0.25-0.5 mmol. Conditions: **1a-c** : allyl alcohol 1.05 : 1, 0.075 M, THF, 0°C-rt

To begin, it was deemed important to utilize ketone reactants that are readily available from inexpensive starting materials. With this in mind, we synthesized precursors using Claisen condensations of α-tetralone with ethyl formate (**1a**), acetic anhydride (**1b**), and propanoic anhydride (**1c**) (Table 1).[42,43] It is important to point out that the simple, high-yielding Claisen condensations yield active methylene compounds that undergo mild acetoacetic ester-type alkylation. With **1a-c** in hand, we screened conditions for DaA. The formyl derivative (**1a**) provided a good yield of allylated product **2a**, but significant quantities of protonation product were also produced. The amount of protonation could be attenuated by use of bidentate *rac*-BINAP (entry 2), but could not be avoided entirely. The protonation product could arise from palladium-catalyzed reduction by formate ion.[44-46] With this in mind, the diketones **1b-c** were subjected to the reaction conditions. Using these ketones, $Pd(PPh_3)_4$ was an active catalyst for DaA and little protonation side reaction took place (Table 1, entries 3-4).

With the reaction conditions in hand, we set out to examine the scope of the DaA reaction (Table 2). Simple allyl and β-substituted allyl alcohols performed well in the reaction (**2a**-**2c**). An acrylate could likewise be incorporated without competing conjugate additions of alkoxide or enolate (**2c**). Unfortunately, low yields were observed with terminally substituted allyl alcohol coupling partners such as cinnamyl alcohol.

Aside from α-methyl substitution such as that in **2a**, allylic systems could be easily incorporated via Tsuji-Trost allylation prior to DaA (**2b**-**2k**). The use of Tsuji-Trost allylation prior to DaA highlights an important advantage of DaA as compared to decarboxylative allylation: The ketone substrates for DaA are compatible with a variety of metal-catalyzed couplings (including Tsuji-Trost) that are incompatible with the allyl ester/carbonate structures required for DcA. Due to the robust nature of the Tsuji-Trost allylation, a diverse pool of bisallylated α-tetralones could be prepared. Related 1,6-heptadienes undergo a wide variety of cycloisomerization and cycloaddition reactions.[32-39] With regard to the R^1 substituent introduced via Tsuji-Trost allylation, terminal (**2g**) and β-aryl (**2d**) substitution on the allyl motif were allowed. Importantly, the synthetically useful cyclopropylallyl (**2h**) moiety could be incorporated, allowing for the rapid synthesis of a unique precursor for [5+2] cycloaddition.[39] Other important allylic acetates could also be incorporated via Tsuji-Trost allylation. For example, crotyl (**2f**), cinnamyl (**2g**), prenyl (**2i**), geranyl (**2k**), and myrtenyl (**2j**) carbon skeletons could be incorporated on to the tetralone scaffold.

Table 2. Racemic DaA

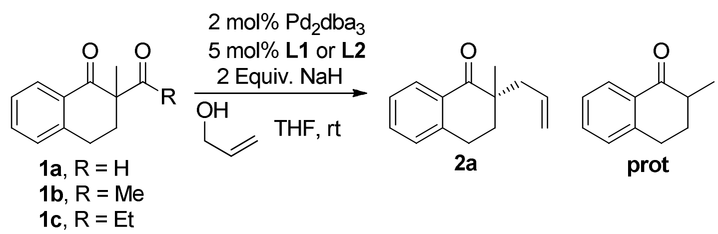


[a] standard conditions: (0.2-0.3 mmol scale) 1:1 acetyltetralone : allyl alcohol, 2 equiv. NaH, 2.5 mol% $Pd(PPh_3)_4$, 12 h, 0.075M [b] ≥0.5 gram scale: 1 mol% $Pd(PPh_3)_4$, 40°C 5-12h, 0.5 M [c] starting material was 4:1 mixture of E/Z crotyl isomers and is reflected in the product [d] standard conditions for 48h [e] 23.5 mmol scale,1:1 acetyl tetralone : allyl alcohol, 1.5 equiv. NaH, THF, 0°C–rt 0.5 M, 16-18h [f] average of 2 runs by 2 different experimenters

Regarding the tetralone core, electron withdrawing (e.g., fluoro, **2l**) and donating (**2m,n**) groups were compatible. Aside from tetralone cores, both indanone (**2o**) and benzosubarone (**2p**) were compatible substrates.

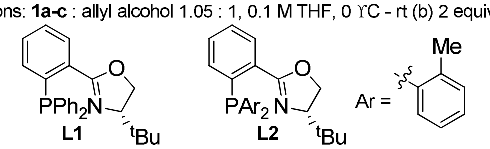
Since the starting materials for DaA are commercially available and/or easily prepared, many of the products in Table 2 were prepared on the > 0.5 gram scale (Table 2, footnote b). To better test the scalability of the DaA reaction, we further developed the protocol for multi-gram synthesis (Table 2, **2q**). We prepared > 6 grams of **2q** using allyl alcohol as a coupling partner and were able to reduce the loadings of Pd (0.5 mol%) and base (1.5 equiv.).

Table 3. Development of asymmetric DaA



Entry	Substrate	Ligand	**2a : prot**	Yield **2a** (%)	ee **2a** (%)
1	**1a**	**L1**	89 : 11	89	79
2	**1b**	**L1**	91 : 9	75	85
3	**1c**	**L1**	95 : 5	95	80
4	**1b**[b]	**L1**	88 : 12	84	66
5	**1a**	**L2**	90 : 10	-	62
6	**1b**	**L2**	95 : 5	-	58

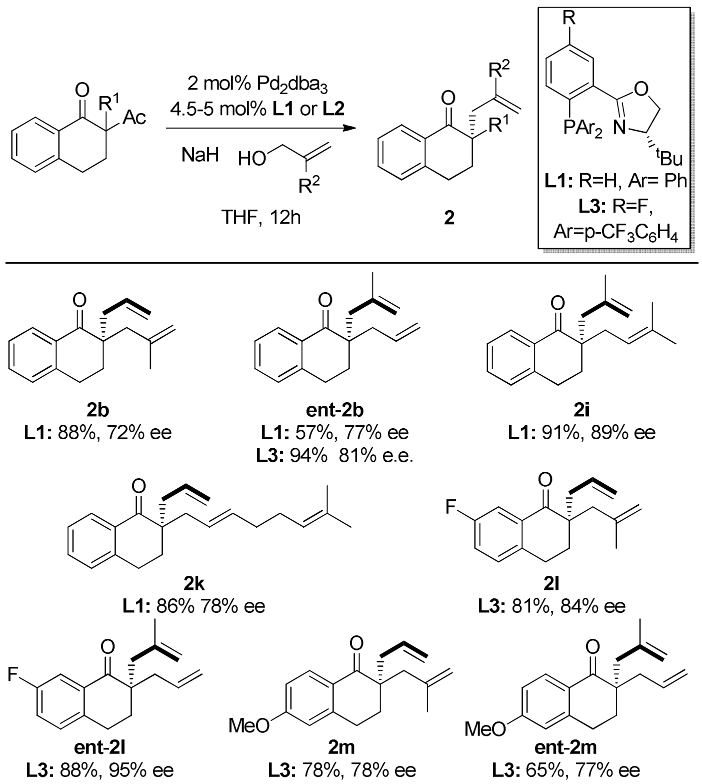
(a) conditions: **1a-c** : allyl alcohol 1.05 : 1, 0.1 M THF, 0 ϒC - rt (b) 2 equiv. allyl alcohol



Next we turned our attention to the development of an asymmetric reaction to synthesize enantioenriched **2a** (Table 3). We were pleased to see that useful ee's (79-85 % ee) could be achieved using the formyl, acetyl, and propanoyl cleaving groups (**1a**-**c**) by utilizing the commercially available ^{t}BuPHOX ligand **L1** (entries 1-3).

While the acetyl group provided the highest ee (entry 2), the enantioselectivity of the coupling was not strongly dependent on the cleaving group. Importantly, excess alkoxide had a detrimental effect on the ee (entry 4) and thus the acetyl tetralone must be used in slight excess (1.05 equiv) compared to alkoxide. One potential explanation for this observation is that excess alkoxide competes with the enolate for coordination to palladium. Such a process would interfere with the inner-sphere mechanism for allylation as proposed by Stoltz.[47] Lastly, commercially available ^{t}BuPHOX derivative **L2** was a significantly poorer ligand (58-62 % ee, entries 5-6) in this transformation.

Table 4. Synthesis of enantioenriched 1,6-dienes via DaA

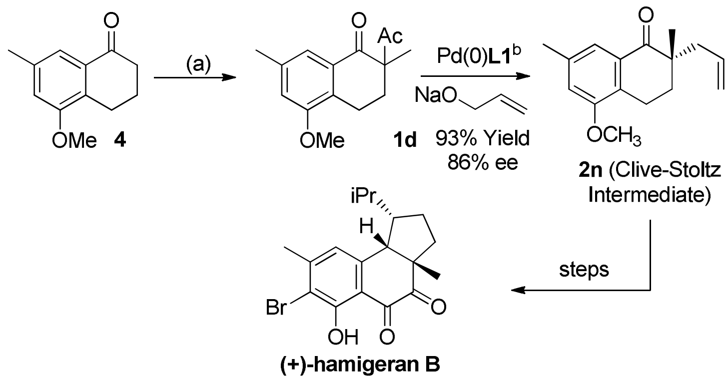


(a) conditions: 0.2-0.3 mmol 1.05 : 1 acetyltetralone : allylic alcohol, 0.075M in THF, 2 equiv. NaH, premix Pd/**L** for 5 min @ 40 °C

To demonstrate the scope of this asymmetric variant, we prepared an assortment of enantioenriched 1,6-heptadienes (Table 4). The 1,6-heptadienes were prepared by 2-step Tsuji-Trost/asymmetric DaA. One advantage of sequential allylation is that *either enantiomer of the product can be prepared by simply interconverting the two allylic coupling partners* (e.g. **2b** and

ent-2b, Table 4). It is noteworthy that the yield and ee of **ent-2b** was superior using the fluorinated *tert*-butyl PHOX ligand **L3**. This type of ligand has been shown by Stoltz to be particularly useful for sluggish allylation reactions.[48,49] In our hands we noticed a similar reaction efficiency increase. As before, important naturally occurring allylic carbon chains such as prenyl (**2i**) and geranyl (**2k**) groups could also be incorporated.

Scheme 3. Synthesis of Clive-Stoltz intermediate **2n** *en route* to (+)-hamigeran



(a) i. Ac_2O, BF_3OEt_2 ii. K_2CO_3, MeI, DMSO, 60% yield (b) 2 eqiuv. NaH, 1 equiv. allyl alcohol THF, 2 mol% Pd_2dba_3 5 mol% **L1**, 0.075M, rt, 24h.

In addition to the heptadiene synthesis, DaA was also utilized to synthesize a key intermediate used for the synthesis of (+)-hamigeran. The synthesis of the Clive-Stoltz intermediate **2n** (Scheme 2) proceeded via acetylation and methylation of the known tetralone **4**. The asymmetric deacylative allylation reaction went without incident providing the required intermediate **2n** in high yield (93%) and ee (86%). DaA provides intermediate **2n** in similar yield and ee to that achieved by Stoltz using *the same ligand under similar conditions*.[50] It is important to point out that Stoltz and coworkers, using a different ligand, can achieve increased ee (91-94%).[50] That said, the DaA route has several advantages. First, the prior methods for preparing **2n**, introduce the α-methyl group by a cryogenic LDA/HMPA mediated methylation.[14,41] Our DaA method allows alkylation under simple K_2CO_3 mediated alkylation conditions. Secondly, the decarboxylative coupling method also requires the 2-step allyl enol carbonate formation (with allyl chloroformate) followed by asymmetric DcA. The DaA method reported herein allows the intermolecular introduction of the allyl group directly from allyl alcohol with the potential for analoging.

To conclude, we have developed a new method for allylic alkylation of α-tetralones via deacylative allylation. The reaction directly couples readily available ketone pronucleophiles with allylic alcohols using facile retro-Claisen cleavage to form reactive intermediates *in situ*. The simplicity and robustness of the reaction conditions is demonstrated by the preparation of > 6 grams of an allylated tetralone in one pot from commercially available materials. Furthermore, use of non-racemic PHOX ligands allows intermolecular formation of quaternary stereocenters directly from allylic alcohols. To demonstrate the utility of this new reaction, enantioenriched 1,6-heptadienes as well as a key intermediate in the synthesis of (+)-hamigeran were prepared.

Experimental Section:

General Experimental Methods

All reactions were run under an argon atmosphere using a Schlenk-argon line, unless noted. $Pd(PPh_3)_4$ and Pd_2dba_3 was purchased from Strem, stored in a glove box and used as is. PHOX ligands were purchased from Aldrich or prepared by the known literature procedures.[48,49] THF was distilled over Na using benzophenone as an indicator. Allyl alcohol and β-methylallyl alcohol were purchased from Aldrich, stored over 3Å MS in a sealed vial equipped with a rubber septum for removal by syringe. Acetyltetralones were prepared by their literature procedure.[42-43] All other substrates were prepared according to the procedures outlined below in the experimental section. 2-acetyltetralone **1** is commercially available from Aldrich. It can also be prepared by the Claisen condensation (see procedure below). **4** was prepared by the literature procedures.[14,41]

Chiral separation was performed on an HPLC instrument using an OD-H chiracel column. Stereochemical configuration is based on Stoltz's assignment as retention times, chiral column (chiracel OD-H), and catalyst ((S)-^{t}BuPHOX) were the same with same products (e.g. **2a**, **2n**).[7,14]

General procedure (small scale) for racemic deacylative allylation: Synthesis of 2a

A flame-dried 10mL Schlenk flask equipped with a stir bar was brought into a glove box and charged with NaH (2 equiv. 0.50, 12mg) and $Pd(PPh_3)_4$ (2.5 mol%, 0.0063 mmol, 7.2 mg). The flask was capped, removed from the glove box and attached to a argon line. 4 mL of dry THF was added to the flask and allyl alcohol (0.25 mmol, 15 mg) and tetralone **1b** (0.255 mmol, 51 mg) were added in that order. Both syringes used to transfer reagents were washed with the reaction mixture solvent and reinjected. The vessel was capped, wrapped in parafilm and the system was completely sealed over argon and allowed to react for 5h.

After the allotted reaction time as determined by TLC (5h), the reaction mixture was diluted with 15% EtOAc in hexanes and filtered through a SiO_2 plug with excess (50-75 mL) of the 15% EtOAc in hexanes solvent mixture. The solvent was evaporated and subjected to silica gel chromatography (3% EtOAc in Hexanes) to yield the pure product **2a**.

General procedure for asymmetric deacylative allylation: synthesis of enantioenriched 2a

Two flame-dried 10mL Schlenk flasks equipped with stir bars were flame dried and brought into a glove box. The catalyst (Pd_2dba_3, 1.25 mol % 0.0063 mmol, 5.7 mg and tert-butylPHOX ligand, 3 mol%, 0.015 mmol, 6 mg) was loaded into one flask and NaH (2 equiv., 1 mmol, 25 mg) was loaded into the other. Both were capped, removed from the glove box and attached to a Schlenk argon line. 2mL of dry THF was added to the catalyst flask, which was then stirred for 10 min at 40 °C. In the meantime, 3 mL of dry THF was added to the flask containing NaH. To the NaH containing flask was added allyl alcohol (via syringe, 0.50 mmol, 29mg) and tetralone derivative **1a** (via syringe, 0.51 mmol, 95mg) in that order. Both syringes used to transfer reagents were washed with the reaction mixture solvent and reinjected. Directly after the final reagent addition, the preformed catalyst was then transferred via syringe and injected as a shot (no need to wash this syringe). The vessel was capped, wrapped in parafilm and the system was completely closed and allowed to react for 5h.

After the allotted reaction time as determined by TLC (12h), the reaction mixture was diluted with 15% EtOAc in hexanes and filtered through a SiO_2 Plug with excess (50-75mL) of the 15% EtOAc in hexanes solvent mixture. The solvent was evaporated and subjected to silica gel chromatography (3% EtOAc in Hexanes) to yield the pure product **2a**.

General procedure (large scale) for deacylative allyation: Synthesis of 2q

A flame-dried 200 mL Schlenk flask was equipped with an egg-shaped stir bar and brought into a glove box where it was charged with NaH (95% purity, 1.5 equiv., 35.3 mmol, 890 mg) and $Pd(PPh_3)_4$ (0.5 mol%, 0.118 mmol, 136 mg). The flask was capped, removed from the glove box, and attached to an argon line. 25 mL of THF was added and the heterogeneous mixture was chilled to 0 °C in an ice bath. Allyl alcohol (23.5 mmol, 1.364 g) was then added neat dropwise over 5 minutes. The flask was allowed to warm to room-temperature, and upon ceased H_2 (g) effervescence, was re-chilled to 0 °C in an ice bath. Substrate ketone (23.5 mmol, 7.14 g) was dissolved in 15 mL of THF and added dropwise over ~5 min. The transfer vessel and syringe were rinsed with 2 x 5 mL portions of dry THF to ensure complete transfer of the ketone to the reaction vessel. The reaction vessel was then sealed, equipped with an empty balloon (a small amount of pressure builds up over time), removed from the ice bath, and allowed to react at room temperature for 16 − 18 h.

After the allotted reaction time, the reaction mixture was diluted with 100 mL of a 1:4 mixture of ethyl acetate and hexanes and filtered through a pad of silica gel using vacuum filtration. The reaction vessel was washed with 4 x 100 mL portions of the ethyl acetate and hexanes mixture. The filtrate was collected and rotary evaporation yielded the crude product.

The crude product was purified by silica gel column chromatography (~ column size 3 cm diameter x 20 cm height, mobile phase ~2 L of 2.0 % EtOAc in hexanes) yielding the desired product as a viscous yellow oil (6.18 g, 87% yield) as well as ~0.8 g of an 85% pure fraction.

General procedure for methylation of diketones:

A 25mL Schlenk flask equipped with a stir bar was charged with anhydrous K_2CO_3 and attached to an argon line. The substrate (2.5 mmol) was added followed by 5 mL of anhydrous DMSO. 500 μL of MeI was then added over 0.5 min. The vessel was capped and stirred for 30 min.

After the allotted reaction time, the reaction mixture was diluted with 15mL of EtOAc and transferred to a seperatory funnel. The vessel was washed with an extra 15mL EtOAc to ensure complete transfer of its contents. The organic layer was washed with 2 x 50mL portions of 1N HCl. The organic layer was dried, evaporated, and subjected to column chromatography to yield the pure methylated ketone.

General procedure 1 for Tsuji-Trost allylation:

In a glove box, a flame-dried Schlenk flask equipped with a stir bar was charged with 1 equiv. NaH and 1 mol% $Pd(PPh_3)_4$. The vessel was capped and removed from the glove box and attached to an argon line. THF (0.2M) was added followed by 2-acetyltetralone (1 equiv.) was added to the flask. After the rapid effervescence, allyl acetate derivative (1.2 equiv.) was added and the reaction was heated at 40 °C until reaction was complete (as monitored by TLC or GC-MS). Following complete coupling, the reaction mixture was transferred to a seperatory funnel, diluted with EtOAc and extracted with 0.5 M HCl (2 x 10 mL) and brine (1 x 20 mL). The organic layer was dried over $MgSO_4$, volatile organics were removed by rotary evaporation and the residue was subjected to column chromatography yielding the pure allylated 2-acetyltetralone derivative.

General procedure 2 for Tsuji-Trost allylation:

In a glove box, a flame-dried Schlenk flask equipped with a stir bar was charged with 1 mol% $Pd(PPh_3)_4$. The vessel was capped and removed from the glove box and attached to an argon line. K_2CO_3 (5 equiv.), DMSO (0.2M) and 2-acetyltetralone (1 equiv.) were added sequentially. While stirring, the allyl acetate derivative (2.5-3 equiv.) was added and the vessel was capped and stirred at 40 °C until reaction completion (as monitored by TLC or GC-MS). Following complete coupling, the reaction mixture was transferred to a seperatory funnel, diluted with EtOAc and extracted with 0.5 M HCl (2 x 10 mL) and brine (1 x 20 mL). The organic layer was dried over $MgSO_4$, volatile organics were removed by rotary evaporation and the residue was subjected to column chromatography yielding the pure allylated 2-acetyltetralone derivative.

Baylis-Hillman synthesis of *tert*-butyl 2-(hydroxymethyl)acrylate:

A 250 mL round-bottom flask equipped with a stir bar was charged with DABCO (50 mmol, 5.6 g). 30 mL of H_2O was then added followed by paraformaldehyde (100 mmol, 3.03 g). MeCN was then added with heating at 80 °C until the reaction mixture is homogeneous (~30 mL). *Tert*-butyl acrylate (50 mmol, 6.4 g, 7.3 mL) was then added as a single shot. The resulting reaction mixture was heated for 2.5 h.

After the allotted reaction time, the reaction mixture was diluted with 100 mL of DCM and transferred to a seperatory funnel. An additional 100 mL DCM is used to wash the reaction vessel to ensure complete transfer. The DCM layer was then washed with 100 mL of 1N HCl followed by brine (50 mL). The volatiles were removed by rotary evaporation and the crude oil was subjected to column chromatography (20% EtOAc in hexanes) to yield the desired product.

2a:[6] Isolated as a yellow oil (0.25 mmol scale, 0.045 g, 90%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (dd, J = 7.9, 1.1 Hz, 1H), 7.39 (td, J = 7.5, 1.4 Hz, 1H), 7.23 (t, J = 7.8 Hz, 1H), 7.15 (d, J = 7.6 Hz, 1H), 5.72 (m, 1H), 5.02 (s, 1H), 5.00 (dm, J = 8.65 Hz, 1H), 2.91 (dd, J = 12.1, 5.1 Hz, 2H), 2.40 (dd, J = 13.8, 7.3 Hz, 1H), 2.21 (ddt, J = 13.8, 7.5, 1.1 Hz, 1H), 2.01 (m, 1H), 1.84 (ddd, J = 13.7, 7.1, 5.5 Hz, 1H), 1.12 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 202.1, 143.3, 133.9, 133.1, 131.6, 128.7, 128.0, 126.6, 118.2, 44.6, 41.1, 33.3, 25.3, 21.9. HPLC: Chiracel OD-H column, mobile phase = Hexanes : 2-propanol 99.7 : 0.3, flow rate = 0.4 μL/min

2b: Isolated as a yellow oil (0.3 mmol scale, 0.049 g, 68%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (dd, J = 7.9, 1.1 Hz, 1H), 7.39 (td, J = 7.5, 1.4 Hz, 1H), 7.24 (t, J = 7.51 Hz, 1H), 7.15 (d, J = 7.6 Hz, 1H), 5.72 (m, 1H), 5.03 (dm, J = 4.61 Hz, 1H), 5.00 (dm, J = 14.02 Hz, 1H), 2.92 (m, 2H), 2.67 (d, J = 13.6 Hz, 1H), 2.44 (dt, J = 13.9, 7.03, 1.03 Hz 1H), 2.16 (m, 2H), 1.98 (ddd, J = 13.9, 8.6, 5.3 Hz, 1H), 1.90 (ddd, J = 14.0, 6.4, 5.3 Hz, 1H), 1.53 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 200.0, 142.1, 141.4, 132.9, 132.1, 131.0, 127.6, 127.1, 125.7, 117.5, 114.0, 46.7, 41.7, 39.1, 29.2, 24.1, 23.4. HRMS data: Calc. for $C_{17}H_{20}O$ (M + H) = 241.1592. Found 241.1581; HPLC: Chiracel OD-H column, mobile phase = hexanes : 2-propanol 99.6 : 0.8, flow rate = 0.4 μL/min

2c: Isolated as a yellow oil (2.0 mmol scale, 0.550 g, 81%) ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (dd, J = 7.9, 1.2 Hz, 1H), 7.38 (td, J = 7.51, 1.4 Hz, 1H), 7.23 (t, J = 7. 73 Hz, 1H), 7.14 (d, J = 7.6 Hz, 1H), 6.09 (d, J = 1.8 Hz, 1H), 5.45 (s, 1H), 4.74 (s, 1H), 4.61 (s, 1H), 3.02 (ddd, J = 17.0, 9.3, 4.8 Hz, 1H), 2.88 (dt, J = 17.05, 5.76 Hz, 1H), 2.74 (d, J = 13.8 Hz, 1H), 2.71 (d, J = 13.8 Hz, 1H), 2.61 (d, J = 13.4 Hz, 1H), 2.08 (m, 1H), 2.02 (d, J = 13.7 Hz, 1H), 1.78 (ddd, J = 14.0, 6.4, 4.9 Hz, 1H), 1.52 (s, 3H), 1.35 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 200.2, 166.9, 143.1, 142.4, 138.3, 133.1, 132.4, 128.6, 128.1, 126.6, 115.4, 80.6, 48.7, 43.9, 36.4, 30.2, 27.9, 25.3, 24.5. HRMS data: Calc. $C_{22}H_{28}O_3$ (M + Na = 363.1936), found 363.1914

2d: Isolated as a yellow oil (0.27 mmol scale, 0.051 g, 62%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (dd, J = 7.9, 1.1 Hz, 1H), 7.35 (td, J = 7.5, 1.4 Hz, 1H), 7.19 (m, 8H), 7.09 (d, J = 7.6 Hz, 1H), 5.63 (m, 1H), 5.20 (d, J = 1.7 Hz, 1H), 5.03 (s, 1H), 4.96 (dm, J = 10.21 1H), 4.90 (dm, J = 17.0, 1.3 Hz, 1H), 2.95 (d, J = 13.9 Hz, 1H), 2.81 (m, 2H), 2.75 (d, J = 13.9 Hz, 1H), 2.43 (dd, J = 14.0, 6.7 Hz, 1H), 2.06 (dd, J = 14.0, 7.9 Hz, 1H), 1.83 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 200.7, 145.5, 142.9, 134.1, 133.0, 132.1, 128.5, 128.2, 128.0, 127.3, 126.6, 126.5, 118.4, 118.1, 48.9, 39.8, 39.5, 30.4, 25.1. HRMS data: Calc. For $C_{22}H_{22}O$ (M + H = 303.174, M + Na = 325.1568), found 303.1710, 325.1540

2e: Isolated as a yellow oil (0.3 mmol scale, 0.061 g, 80%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (dd, J = 7.9, 1.2 Hz, 1H), 7.38 (td, J = 7.5, 1.4 Hz, 1H), 7.23 (t, J = 7.34 Hz, 1H), 7.14 (d, J = 7.6 Hz, 1H), 5.70 (m, 1H), 5.04 (m, 1H), 5.00 (s, 1H), 4.97 (m, 1H), 2.91 (t, J = 6.4 Hz, 2H), 2.46 (ddt, J = 14.14, 6.45, 1.45 Hz, 1H), 2.32 (dd, J = 14.6, 7.0 Hz, 1H), 2.19 (ddd, J = 14.0, 9.2, 8.2 Hz, 2H), 1.96 (t, J = 6.41 Hz, 2H), 1.63 (s, 3H), 1.50 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 201.3, 143.2, 134.4, 134.3, 133.0, 132.0, 128.7, 128.0, 126.6, 119.2, 118.0, 48.5, 39.3, 33.1, 30.5, 26.1, 25.2, 18.0. HRMS data: Calc. for $C_{18}H_{22}O$ (M + H = 255.1749), Found 255.1732; Chiral Resolution: Chiracel OD-H column, mobile phase = hexanes : 2-propanol 99.7 : 0.3, flow rate = 0.4 μL/min

2f: Isolated as a yellow oil (2.06 mmol scale, 0.441 g, 84%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, J = 8.14 Hz, 1H), 7.38 (td, J = 7.5, 1.4 Hz, 1H), 7.23 (t, J = 7.6 Hz, 1H), 7.14 (d, J = 7.7 Hz, 1H), 5.41 (m, 1H), 5.33 (m, 1H), 4.73 (s, 1H), 4.60 (s, 1H), 2.91 (m, 2H), 2.66 (d, J = 13.7 Hz, 1H), 2.35 (dd, J = 14.22, 6.81 Hz, 1H), 2.10 (m, 2H), 1.92 (m, 2H), 1.59 (dd, J = 6.2, 1.2 Hz, 2H), 1.52 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 201.3, 143.2, 142.7, 133.1, 133.0, 132.1, 129.1, 128.6, 128.1, 126.7, 126.6, 126.1, 114.9, 114.9, 47.9, 42.7, 38.8, 30.0, 25.2, 24.5, 18.1. HRMS data: Calc. for $C_{18}H_{22}O$ (M + H = 255.1748 and M + Na = 277.1568) found 255.1713 and 277.1593.

2g: Isolated as a yellow oil (0.20 mmol scale, 0.049g, 77%) ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (dd, J = 7.9, 1.2 Hz, 1H), 7.40 (td, J = 7.5, 1.4 Hz, 1H), 7.26 (m, 3H), 7.21 (t, J = 7.43 Hz, 2H), 7.13 (m, 2H), 6.36 (d, J = 15.7 Hz, 1H), 6.12 (m, 1H), 4.76 (s, 1H), 4.63 (s, 1H), 2.95 (dd, J = 12.3, 6.0 Hz, 2H), 2.69 (d, J = 13.6 Hz, 1H), 2.63 (ddd, J = 14.0, 7.2, 1.3 Hz, 1H), 2.31 (ddd, J = 14.0, 7.8, 1.1 Hz, 1H), 2.20 (d, J = 13.7 Hz, 1H), 1.99 (m, 2H), 1.56 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 201.1, 143.1, 142.3, 137.4, 133.5, 133.2, 132.0, 128.7, 128.5, 128.1, 127.2, 126.7, 126.1, 125.8, 115.2, 48.3, 43.0, 39.4, 30.5, 25.3, 24.5.

HRMS data: Calc. $C_{23}H_{24}O$ (M + H = 317.1905), found 317.1911

2h: Isolated as a yellow oil (2.0 mmol scale, 0.449 g, 80%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (dd, J = 7.9, 1.1 Hz, 1H), 7.38 (td, J = 7.5, 1.4 Hz, 1H), 7.23 (t, J = 7.5 Hz, 1H), 7.14 (d, J = 7.6 Hz, 1H), 5.39 (dt, J = 14.9, 7.4 Hz, 1H), 4.94 (dd, J = 15.1, 8.6 Hz, 1H), 4.72 (dd, J = 2.1, 1.5 Hz, 1H), 4.61 (s, 1H), 2.90 (m, 2H), 2.66 (d, J = 13.6 Hz, 1H), 2.35 (ddd, J = 14.0, 7.1, 1.1 Hz, 1H), 2.12 (d, J = 13.7 Hz, 1H), 2.07 (ddd, J = 14.1, 7.6, 0.9 Hz, 1H), 1.92 (m, 2H), 1.54 (s, 3H), 1.28 (m, 1H), 0.58 (m, 2H), 0.24 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 201.3, 143.2, 142.6, 138.2, 133.0, 132.1, 128.6, 128.1, 126.6, 122.5, 114.9, 48.0, 42.7, 38.7, 30.0, 25.2, 24.5, 13.7, 6.6, 6.5.

HRMS data: Calc. for $C_{20}H_{24}O$ (M + H = 281.1905), Found 281.1918

2i: Isolated as a yellow oil (2.95 mmol scale, 0.523 g, 66%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 (dd, J = 7.9, 1.1 Hz, 1H), 7.38 (td, J = 7.5, 1.4 Hz, 1H), 7.23 (t, J = 7.32 Hz, 1H), 7.14 (d, J = 7.7 Hz, 1H), 5.07 (m, 1H), 4.72 (s, 1H), 4.60 (s, 1H), 2.90 (m, 2H), 2.69 (d, J = 13.6 Hz, 1H), 2.30 (dd, J = 14.7, 6.9 Hz, 1H), 2.15 (m, 1H), 2.11 (d, J = 13.7 Hz, 1H), 1.93 (m, 2H), 1.64 (s, 3H), 1.53 (s, 3H), 1.51 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 201.5, 143.2, 142.7, 134.7, 133.0, 132.1, 128.6, 128.1, 126.6, 119.2, 114.8, 48.4, 42.7, 33.96, 29.9, 26.1, 25.3, 24.5, 18.1. HRMS data: Calc. for $C_{19}H_{24}O$ (M + Na = 291.1724), found 291.1693; Chiral Resolution: Chiracel OD-H column, mobile phase = Hexanes : 2-propanol 99.7 : 0.3, flow rate = 0.4 µL/min 17.95 min. and 18.45 min.

2j: Isolated as a yellow oil (1.9 mmol scale, 0.604 g, 95%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (m, 1H), 7.38 (t, J = 7.6 Hz 1H), 7.23 (t, J = 7.6 Hz, 1H), 7.14 (d, J = 7.6 Hz, 1H), 5.22 (s, 1H), 4.70 (m, 1H), 4.59 (d, J = 6.8 Hz, 1H), 2.98 (m, 1H), 2.87 (m, 1H), 2.73 (d, J = 13.6 Hz, 1H), 2.37 (d, 1H), 2.03 (m, 9H), 1.51 (s, 2H), 1.18 (s, 2H), 0.77 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 201.3, 144.0, 143.2, 143.1, 143.0, 133.0, 132.9, 132.4, 128.6, 128.5, 128.1, 128.1, 126.6, 126.6, 122.6, 122.5, 114.9, 114.8, 48.9, 48.0, 47.4, 43.7, 43.6, 43.3, 43.0, 40.4, 40.2, 37.9, 31.8, 31.8, 31.7, 31.7, 29.8, 29.4, 26.4, 26.4, 25.6, 25.5, 24.6, 24.6, 21.3, 21.3. HRMS data: Calc. for $C_{24}H_{30}O$ (M + H = 335.2374 and M + Na = 357.2194), found 335.2338 and 357.2197.

2k: Isolated as a yellow oil (0.3 mmol scale, 0.085 g, 88%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (dd, J = 7.9, 1.1 Hz, 1H), 7.38 (td, J = 7.5, 1.4 Hz, 1H), 7.23 (t, J = 7.4 Hz, 1H), 7.14 (d, J = 7.6 Hz, 1H), 5.70 (m, 1H), 5.06 (t, J = 7.35 1H), 4.99 (s, 1H), 4.97 (m, 2H), 2.90 (t, J = 6.3 Hz, 2H), 2.45 (dd, J = 13.9, 7.0 Hz, 1H), 2.33 (dd, J = 14.6, 7.0 Hz, 1H), 2.19 (m, 2H), 1.96 (m, 6H), 1.54 (s, 3H), 1.52 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 201.3, 143.3, 137.9, 134.3, 133.0, 132.0, 131.4, 128.6, 128.0, 126.6, 124.3, 119.3, 118.0, 48.6, 40.0, 39.3, 33.0, 30.4, 26.5, 25.7, 25.3, 17.7, 16.3. HRMS Data: $C_{23}H_{31}O$ (M + H = 323.2375) found, 323.2364. **Chiral Resolution:** Chiracel OD-H column, mobile phase = Hexanes : 2-propanol 99.7 : 0.3, flow rate = 0.4 µL/min

2l: Isolated as a yellow oil (0.3 mmol scale, 0.054 g, 70%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (dd, J = 9.3, 2.7 Hz, 1H), 7.11 (m, 2H), 5.70 (ddt, J = 17.3, 10.2, 7.3 Hz, 1H), 5.01 (m, 2H), 4.75 (s, 1H), 4.61 (s, 1H), 2.87 (m, 2H), 2.65 (d, J = 13.7 Hz, 1H), 2.42 (dd, J = 14.0, 7.1 Hz, 1H), 2.15 (m, 2H), 1.93 (m, 2H), 1.52 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 200.0, 161.7 (d, 249.9 Hz), 142.2, 138.8 (d, J = 2.97 Hz), 133.6, 130.5 (d, J = 7.03 Hz 120.55 (d, J = 22.21 Hz), 118.7, 115.3, 113.9 (d, J = 22.0 Hz), 47.5, 42.7, 40.0, 30.3, 24.5, 24.4. HRMS data: $C_{17}H_{19}FO$ (M + Na = 281.1318) found, 281.1322. **Chiral Resolution:** Chiracel OD-H column, mobile phase = Hexanes : 2-propanol 99.9 : 0.1, flow rate = 0.4 μL/min

2m: Isolated as a yellow oil (0.3 mmol scale, 0.045 g, 55%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (d, J = 8.8 Hz, 1H), 6.76 (dd, J = 8.8, 2.5 Hz, 1H), 6.59 (d, J = 2.5 Hz, 1H), 5.72 (m, 1H), 5.02 (dm, J = 3.29 Hz 1H), 4.99 (dm, J = 11.31 Hz 1H), 4.73 (s, 1H), 4.61 (s, 1H), 3.78 (s, 3H), 2.88 (m, 2H), 2.67 (d, J = 13.6 Hz, 1H), 2.42 (dd, J = 14.0, 7.0 Hz, 1H), 2.15 (m, 1H), 2.11 (d, J = 13.7 Hz, 1H), 1.95 (ddd, J = 14.0, 8.9, 5.2 Hz, 1H), 1.88 (ddd, J = 14.0, 8.9, 5.2 Hz 1H), 1.53 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 199.8, 163.4, 145.6, 142.6, 134.1, 130.6, 125.7, 118.3, 114.9, 113.3, 112.3, 55.4, 47.4, 42.9, 40.4, 30.2, 25.6, 24.4.

HRMS data: $C_{18}H_{22}O_2$ (M + Na = 293.1517), found 293.1545. **Chiral Resolution:** Chiracel OD-H column, mobile phase = Hexanes : 2-propanol 99.7 : 0.3, flow rate = 1 μL/min

2n:[14,41] Isolated as a yellow oil (0.25 mmol scale, 0.046 g, 75%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (s, 1H), 6.76 (s, 1H), 5.71 (ddt, J = 16.6, 10.5, 7.4 Hz, 1H), 5.01 (m, 1H), 4.98 (dm, J = 9.53 Hz, 1H), 3.78 (s, 3H), 2.76 (m, 2H), 2.35 (dd, J = 13.8, 7.3 Hz, 1H), 2.30 (s, 3H), 2.18 (dd, J = 13.8, 7.5 Hz, 1H), 1.95 (ddd, J = 13.6, 7.1, 5.4 Hz, 1H), 1.80 (m, 1H), 1.09 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 202.6, 156.6, 136.8, 134.1, 132.1, 129.4, 119.6, 118.1, 115.0, 55.6, 44.3, 40.9, 32.8, 21.8, 21.5, 18.9. Chiral Resolution: Chiracel OD-H column, mobile phase = Hexanes : 2-propanol 99.7 : 0.3, flow rate = 0.4 μL/min.

2o:[6] Isolated as a yellow oil (0.45 mmol scale, 0.074 g, 88%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (d, *J* = 7.7 Hz, 1H), 7.39 (td, *J* = 7.5, 1.1 Hz, 1H), 7.22 (d, *J* = 7.7 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 5.45 (m, 1H), 4.87 (d, *J* = 17.0 Hz, 1H), 4.81 (d, *J* = 10.1 Hz, 1H), 2.97 (d, *J* = 17.2 Hz, 1H), 2.64 (d, *J* = 17.2 Hz, 1H), 2.19 (ddt, *J* = 13.6, 6.7, 1.2 Hz, 1H), 2.10 (dd, *J* = 13.7, 8.0 Hz, 1H), 1.02 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 210.8, 152.6, 135.9, 134.9, 133.9, 127.4, 126.6, 124.3, 118.4, 48.8, 42.5, 39.4, 23.8.

2p:[6] Isolated as a yellow oil (2.5 mmol scale, 0.496 g, 93%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (m, 1H), 7.27 (dd, J = 4.9, 0.9 Hz, 2H), 7.13 (d, J = 7.5 Hz, 1H), 5.75 (ddt, J = 16.3, 10.7, 7.5 Hz, 1H), 5.07 (m, 1H), 5.04 (dm, J = 8.97 Hz, 1H), 2.80 (m, 2H), 2.34 (ddd, J = 7.1, 3.2, 2.1 Hz, 2H), 1.93 (m, 2H), 1.78 (m, 1H), 1.62 (m, 2H), 1.20 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 214.4, 141.6, 137.2, 133.7, 130.7, 128.4, 127.1, 126.5, 118.3, 49.1, 43.9, 34.5, 32.9, 22.8, 22.3.

2q: Isolated as a yellow oil (23.5 mmol scale, 6.2 g, 86%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (dd, J = 7.9, 1.1 Hz, 1H), 7.39 (td, J = 7.5, 1.4 Hz, 1H), 7.23 (m, 5H), 7.12 (m, 2H), 6.35 (d, J =

15.8 Hz, 1H), 6.12 (m, 1H), 5.73 (m, 1H), 5.03 (dd, J = 3.2, 2.0 Hz, 1H), 5.00 (ddd, J = 4.5, 2.0, 1.2 Hz, 1H), 2.93 (m, 2H), 2.62 (ddd, J = 14.0, 7.2, 1.3 Hz, 1H), 2.47 (dd, J = 14.0, 7.1 Hz, 1H), 2.34 (ddd, J = 14.0, 7.8, 1.1 Hz, 1H), 2.25 (dd, J = 14.0, 7.5 Hz, 1H), 2.01 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 200.9, 143.2, 137.4, 133.8, 133.3, 133.2, 131.8, 128.7, 128.5, 128.1, 127.2, 126.7, 126.1, 125.8, 118.4, 48.3, 39.3, 38.5, 30.7, 25.2.

HRMS data: Calc. for $C_{22}H_{23}O$: (M + H = 303.1749), Found 303.1729

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Supporting Information Available

Additional experimental procedures, ^{1}H NMR and ^{13}C NMR reprints available for all compounds herein. This material is available free of charge *via* the Internet at http://pubs.acs.org/.

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