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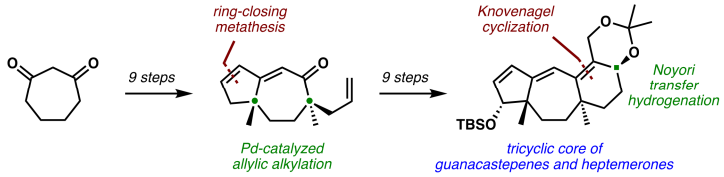

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Development of a catalytic enantioselective synthesis of the guanacastepene and heptemerone tricyclic core

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ABSTRACT

For nearly two decades, synthetic chemists have been fascinated by the structural complexity and synthetic challenges afforded by the guanacastepene and heptemerone diterpenoids. Numerous synthetic approaches to these compounds have been reported, but to date the application of enantioselective catalysis to this problem has not been realized. Herein we report an enantioselective synthesis of an advanced intermediate corresponding to the tricyclic core common to the guanacastepenes and heptemerones. Highlights of this work include sequential Pd-catalyzed decarboxylative allylic alkylation reactions to generate the two all carbon quaternary stereocenters, the use of ring-closing metathesis to close the A ring in the presence of a distal allyl sidechain, and a regio- and diastereoselective oxidation of an trienol ether to introduce oxygenation on the A ring.

1. Introduction

The guanacastepenes are a family of diterpenoids (Figure 1) originally isolated by Clardy and coworkers from an unidentified fungus that was found growing on a tree, *Daphnopsis americana*, in Costa Rica.[1] Various members of the family have displayed interesting anticancer[2] and antibacterial[3] activity. In 2005, Sterner and co-workers reported the isolation of structurally similar diterpenoids, the heptemerones, from the mushroom *Coprinus heptemerus*.[4] Structurally, the guanacastepenes and heptemerones are interesting due to their unusual 5-7-6 ring system with a highly oxidized upper portion and fully saturated lower half. Of particular note are the two quaternary carbon stereocenters that have proven to be the one of the biggest synthetic challenges posed by these targets.

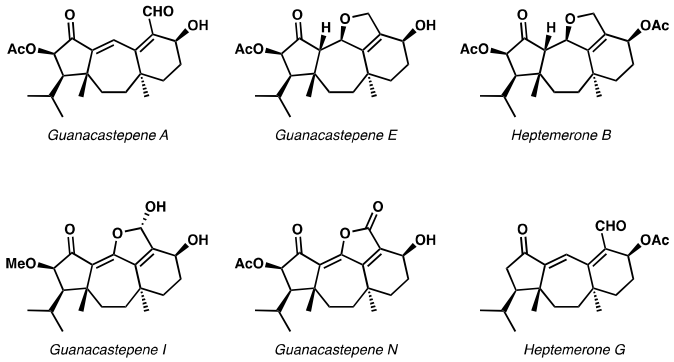


Figure 1. Representative members of the guanacastepene and heptemerone diterpenoids.

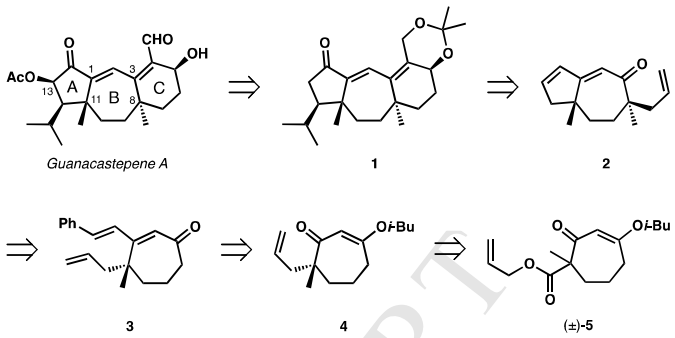
Although initial excitement over this family of natural products has tempered, due to their hemolytic activity,[5] the synthetic community continues to demonstrate interest in these molecules.[6,7] While there have been several nonasymmetric and asymmetric total syntheses of these molecules, no catalytic enantioselective routes have been described in the literature. When our work on these targets started, our group had recently disclosed a series of asymmetric Pd-catalyzed decarboxylative allylic alkylation reactions capable of constructing all-carbon quaternary stereocenters with high levels of stereocontrol.[8] At the same time, we had a burgeoning interest in deploying this technology in natural product synthesis,[9] and believed these targets would be an ideal challenge for this newly developed technology. Herein, we describe our enantioselective synthesis of the tricyclic core common to the guanacastepenes and heptemerones.

2. Results and Discussion

2.1. Synthetic plan

We planned to use keto-acetonide **1** (Scheme 1) as our initial synthetic target owing to Danishefsky and co-workers' success in accessing (±)-guanacastepene A from this intermediate.[10] The acetonide-protected diol would arise through reduction of the corresponding ketoester. We envisoned that the six-membered ring of **1** could be constructed through a Knoevenagel condensation, after chain elongation of the allyl moiety of **2**, while the isopropyl-substituted cyclopentanone moiety would be constructed from the cyclopentene portion of **2**. The α-quaternary stereocenter in **2** would be installed by a Pd-catalyzed decarboxylative allylic alkylation, while the five-membered ring could be closed by ring-closing metathesis (RCM) of **3**. The styryl moiety in cycloheptenone **3** would be installed by performing Stork–Danheiser chemistry on vinylogous ester **4**.[11] Ultimately, an asymmetric decarboxylative allylic alkylation of β-ketoester (±)-**5** would serve as the source of asymmetry in our synthesis.

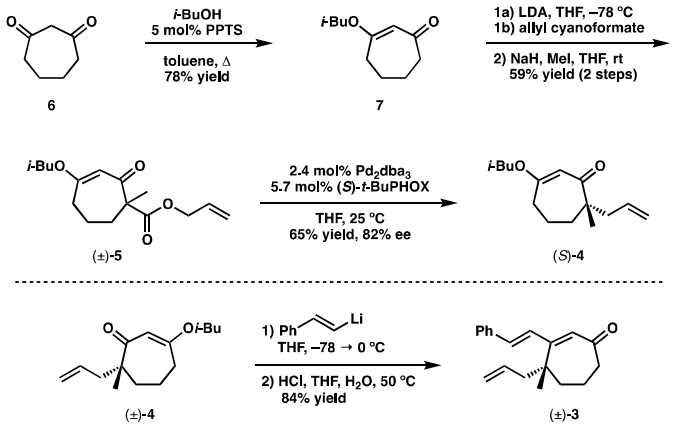
Scheme 1.



2.2. Installation of first stereocenter

Reaction of 1,3-cycloheptanedione (**6**)[12] with isobutanol under Dean–Stark conditions in the presence of PPTS produced vinylogous ester **7** (Scheme 2). Although vinylogous esterification proceeded smoothly, a significant amount of the retro-Dieckmann product was obtained if the generated water was not efficiently removed. This side product could be eliminated with two simple procedural modifications. First, the isobutanol should be distilled from CaO. Second, the heating bath should be preheated before addition of the reaction mixture. Acylation of **7** with allyl cyanoformate, and subsequent methylation, gave the required β-ketoester (±)-**5**. It should be noted at this point that the absolute configuration of the natural products requires the use of (*R*)-*t*-BuPHOX, which is derived from the unnatural enantiomer of *tert*-leucine. Consequently, much of the subsequent work was carried out with racemic material obtained by using PPh_3 as the ligand. We also used the more readily available (*S*)-*t*-BuPHOX to demonstrate that the planned enantioselective decarboxylative allylic alkylation could proceed in good yield and acceptable enantioselectivity [(±)-**5**→(*S*)-**4**].

Scheme 2.

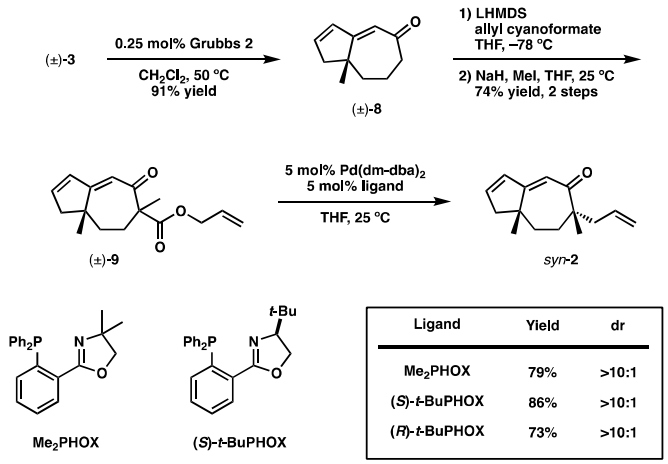


Addition of β-lithiosytrene to vinylogous ester **4** afforded cycloheptenone **3** (Scheme 2). In contrast to what is observed when performing Stork–Danheiser chemistry on six-membered rings, the intermediate β-hydroxy cycloheptanone was found to be particularly stable.[13] Fortunately, warming with aqueous HCl was sufficient to push the elimination toward **3**. Attempts were made to derivatize **3** (e.g. oxime, semicarbazone, various hydrazones) in order to affect enantioenrichment through recrystallization; unfortunately none were successful in forming suitably crystalline products. Fortunately, however, further transformations would make such enrichment unnecessary.

2.3. Installation of second stereocenter

Ring-closing metathesis (RCM) with the second-generation Grubbs catalyst afforded bicyclic dieneone **8**, which was acylated and methylated to give alkylation substrate **9**. When screening ligands to promote the Pd-catalyzed alkylation reaction, we found that the use of an achiral phosphinooxazoline (PHOX) ligand or *either antipode* of *t*-BuPHOX resulted in the formation of a single diastereomer of **2** in all cases. Unfortunately, comparison with later synthetic intermediates revealed this to be the undesired *syn*-methyl diastereomer (*syn*-**2**).

Scheme 3.



Ligand	Yield	dr
Me_2PHOX	79%	>10:1
(*S*)-*t*-BuPHOX	86%	>10:1
(*R*)-*t*-BuPHOX	73%	>10:1

Molecular modeling of the enolate intermediate derived from ketone **9** (enolate **A**) was performed in order to understand the high degree of diastereoselectivity observed in this reaction (Figure 2). This effort revealed that the methyl group of the previously installed quaternary stereocenter sits in a pseudoaxial position and effectively blocks the *Re* face of the enolate. This is in excellent agreement with related computational work by Houk that was reported after our experimental work was completed.[14,15] Houk's work also revealed that steric effects, rather than torsional effects,[16] were primarily responsible for the observed stereoselectivity.

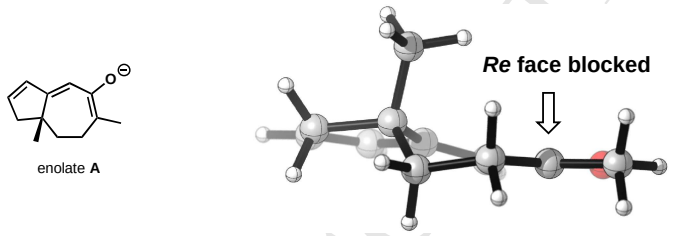
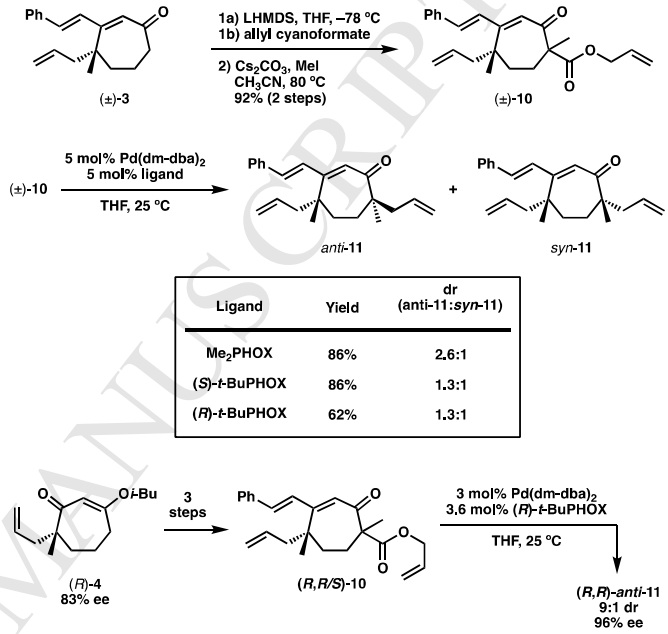


Figure 2. Calculated (B3LYP/6-31+G(d), SMD^{THF}) structure of enolate **A**.

Clearly the large amount of substrate control imposed by enolate **A** would be difficult to overcome using a bicyclic scaffold. However, we believed diminished substrate control might be experienced with a monocyclic enolate.[17] To test this hypothesis, ketone **3** was converted to β-ketoester **10** (Scheme 4). Subjecting ketoester **10** to Pd-catalyzed decarboxylative allylic alkylation, in the presence of an achiral PHOX ligand, afforded ketone **11** with a diastereomeric ratio of 2.6:1. Using either antipode of *t*-BuPHOX resulted in a dr of 1.3:1. It should be emphasized that these results were obtained using material derived from *racemic* ketone **3**. This means that if we were to observe complete catalyst control, the best possible dr we could see with (*S*)- or (*R*)-*t*-BuPHOX is 1:1. With this in mind, the diastereoselectivity afforded by (*S*)- and (*R*)-*t*-BuPHOX was actually quite encouraging.[18]

With this result in hand, ketone (*R*)-**4**, of 83% ee, was prepared using (*R*)-*t*-BuPHOX and advanced to β-ketoester (*R,R*/*S*)-**10**. Performing the second Pd-catalyzed allylic alkylation with (*R*)-*t*-BuPHOX furnished ketone (*R,R*)-**11** with 9:1 diastereoselectivity. Furthermore, the major diastereomer was formed with improved levels of enantiopurity (96% ee), in accordance with the Horeau principle.[19] Because both stereocenters of **11** were formed through catalyst control using the same antipode of the ligand, we are confident that the major diastereomer has the desired *anti*-methyl relationship. Additionally, subsequent RCM furnished a bicyclic compound that was diastereometic to **2**, *vide infra*.

Scheme 4.

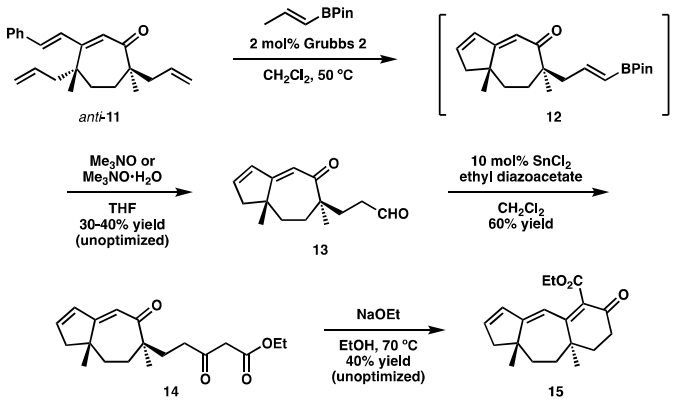


Ligand	Yield	dr (anti-11:*syn*-11)
Me_2PHOX	86%	2.6:1
(*S*)-*t*-BuPHOX	86%	1.3:1
(*R*)-*t*-BuPHOX	62%	1.3:1

2.4. Elaboration of the allyl group and Knoevenagel cyclization

With the two quaternary stereocenters in place, our attention turned to completing the tricyclic ring system (Scheme 5). First, treating compound **11** with the second-generation Grubbs catalyst affected the closure of the A ring. Once the initial RCM reaction was complete, the indicated propenyl boronic ester[20] was added to the reaction mixture in order to carry out a cross metathesis with the remaining allyl group. Undesired cross metathesis with the liberated styrene was minimized by carefully monitoring (TLC) the initial RCM. The resulting boronic ester (**12**) was not isolated. Instead it was immediately oxidized to aldehyde **13** with anhydrous[21] Me_3NO.[22] A number of other cross metathesis partners were also examined, but none proved to be as useful or successful as the coupling with the vinyl boronate.

Scheme 5.



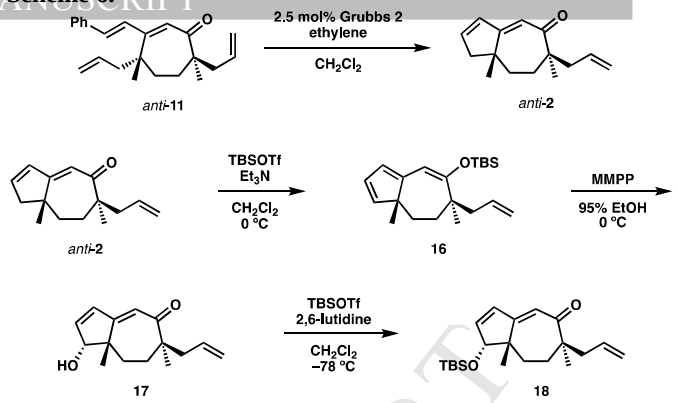
Aldehyde **13** was then coupled to ethyl diazoacetate[23] to furnish β-ketoester **14**. To our delight, heating **14** with NaOEt affected the Knoevenagel cyclization[10] needed to produce tricycle **15** representing the complete guanacastepene ring skeleton. It should be noted the reactions presented in Scheme 3 were not optimized at this point. Nevertheless, they serve as a useful guide for how the tricyclic ring system can be constructed.

2.5. Oxygenation of the A-ring.

Having identified a serviceable route to the tricyclic ring system, we then concerned ourselves with oxidizing the cyclopentene ring. Considerable effort was expended on this particularly troublesome task. We investigated a number of conditions including regioselective epoxidations, dihydroxylations, and allyic oxidations, but all resulted in either no reaction or general decomposition of the starting material. Our prospects for carrying out this necessary transformation seemed bleak until we located a useful procedure from the literature. Kirk and Wiles found that α,β-unsaturated ketones could be converted into γ-hydroxylated ketones by utilizing a two-step procedure involving extended enol ether formation, followed by *m*-CPBA oxidation and hydrolysis.[24,25,26] The authors found that solvent choice was critical to the regioselectivity, as use of CH_2Cl_2 or other anhydrous organic solvents resulted in oxidation at the α-position. Conversely, the use of aqueous organic solvents (e.g. THF, dioxane, EtOH) along with slow addition of the oxidant provided the γ-hydroxy enone in good yields.[24]

Applying these conditions to the present case proved to be particularly rewarding (Scheme 6). First, an RCM was used to convert *anti*-**11** into *anti*-**2**. Careful monitoring of the reaction was needed in order to minimize competitive cross metathesis reactions (homodimer and styrene cross product) involving the allyl sidechain present in **2**. Performing the reaction under an atmosphere of ethylene further minimized these pathways. Treating ketone **2** with TBSOTf furnished silyl enol ether **16**. To our delight, oxidation of **16** with *m*-CPBA in 95% EtOH smoothly formed alcohol **17** in high yield and as the only observed isomer. Through experimentation it was found that magnesium monoperoxyphthalate (MMPP) performed better than *m*-CPBA in this oxidation. The secondary alcohol was then converted to TBS ether **18**.

Scheme 6.

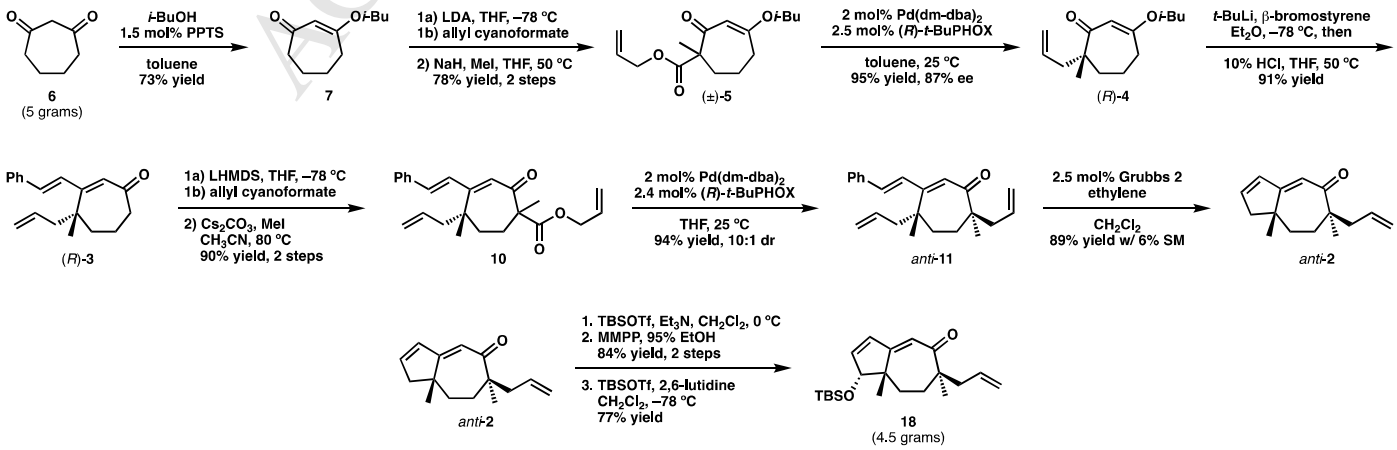


2.6. Multigram synthetic route

Having finally succeeded in identifying conditions to oxygenate the cyclopentene ring, we then scaled up the route with enantioenriched material. Our final optimized route to compound **18** is shown in Scheme 7. Gratifyingly, many of the steps could be scaled with little problem, but there were a few last minute optimizations made along the way. The solvent of the initial decarboxylative allylic alkylation was changed from THF to toluene. This allowed for the relatively small increase in selectivity from 83% to 87% ee. Other notable details include the use of freshly prepared LHMDS for the acylation of **3** and using Cs_2CO_3, rather than NaH, for the subsequent methylation in order to improve the impurity profile of these particular transformations.

The conversion of **4** to **3** was the one step that did need some more optimization. While the lithium-halogen exchange of β-bromostyrene proceeded readily on small scale in THF, the large-scale reaction proceeded to give products of phenylacetylene addition (e.g. deprotonation of α-hydrogen, elimination of bromide, deprotonation of phenylacetylene). Presumably, this was due to inefficient cooling of the exothermic lithium-halogen exchange reaction when performed in large volumes of THF. Changing the solvent to Et_2O alleviated this problem. However, attempts to heat the mixture of Et_2O with aqueous HCl to affect elimination of the hydroxyl group were unsuccessful, presumably due to the two-phase nature of the system. This could be overcome by first quenching the reaction with 10% HCl followed by removal of the volatiles under rotary evaporation. THF was then added and the mixture warmed to 50 ºC. By employing this procedure, **3** was formed in high yield on multigram scale. By following this 12-step route, and starting with 5.0 g of cycloheptanedione, we were able to synthesize 4.5 g of **18** as a pure, colorless oil.

Scheme 7.

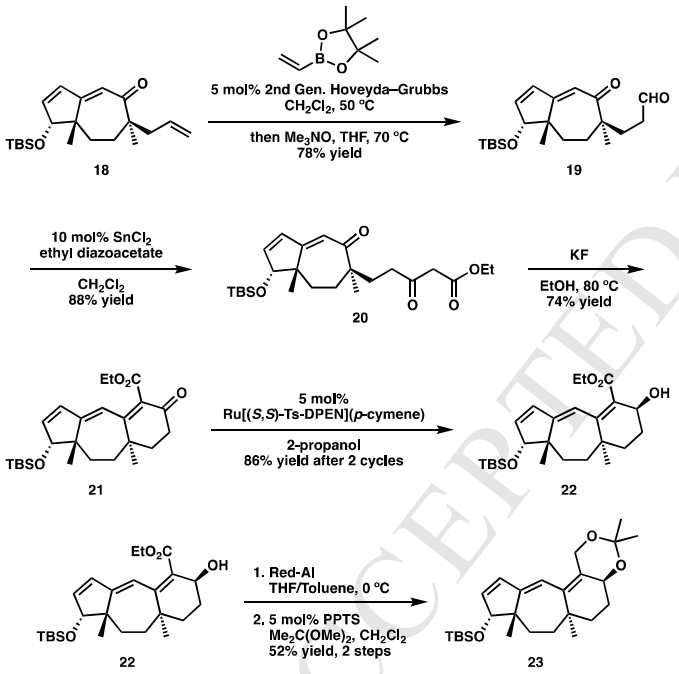


2.7. Generation of tricyclic core

With multigram quantities of **18** in hand, we then had a difficult choice to make. Either we could take the time to elaborate the five membered ring into the required isopropyl-containing cyclopentanone, or investigate that problem after forming the six-membered ring. For better or worse, we chose the latter.

Starting with intermediate **18**, a cross metathesis reaction was performed between the allyl group and the indicated vinyl boronate (Scheme 8). The resulting boronic ester was not isolated. Instead it was immediately oxidized to aldehyde **19** with anhydrous Me_3NO. The aldehyde was then coupled to ethyl diazoacetate[23] to furnish β-ketoester **20**. Preliminary attempts at using an alkoxide base (NaOEt) to affect the desired Knoevenagel ring closure were successful,[10] but we found that using KF as the base[27] provided higher yields. Notably, the use of a protic solvent prevented cleavage of the TBS ether. Finally, stereoselective reduction of the β-ketoester, to give alcohol **22**, was accomplished using a Noyori transfer hydrogenation.[28] By relying on reagent control of the newly formed stereocenter, we were able to address the low diastereoselectivity (~4:1) observed by Danishefsky,[10] Snider,[29] and Wicha.[7h] Ester **22** was then converted into acetonide **23** using standard methods.

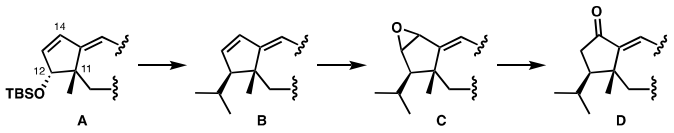
Scheme 8.



2.8. Attempts to functionalize the A ring

With acetonide **23** in hand, we turned our attention to functionalizing the A ring (Scheme 9). We thought that the allylic ether already present in the A ring (**A**) contained enough functionality to allow for installation of the C12 isopropyl group (**B**). Following that, we planned to access the C14 ketone through isomerization of a C13-C14 epoxide (**B**→**C**→**D**). In this manner, and by starting with acetonide **23**, we would generate the same intermediate ketone (**1**) used by Danishefsky and co-workers in their synthesis of guanacastepene A.[10] This same intermediate would also be directly applicable to heptemerone G.[7h]

Scheme 9.

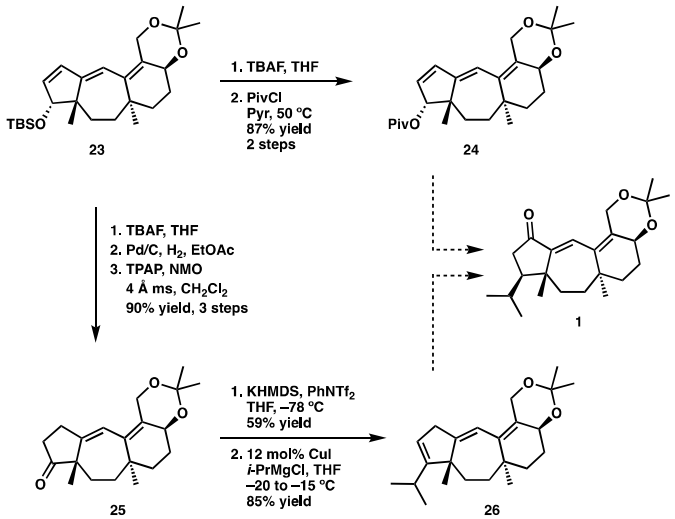


As the silyl ether at C12 was positioned on the α-face, we first considered using a Cu-catalyzed coupling reaction with *i*-PrMgCl. Similar coupling reactions, albeit not as sterically crowded as the present example, have been shown to proceed with net inversion of the initial stereocenter.[30,31] If successful, this would install the C12 isopropyl group with the correct relative configuration. Conversion of silyl ether **23** into allyl pivalate **24** proceeded smoothly (Scheme 10), but all cross coupling attempts with this intermediate failed. This is likely due to the presence of the adjacent quaternary carbon.

In an effort to relieve steric crowding, we decided to convert silyl ether **23** into a vinyl triflate. First, the silyl ether was cleaved using TBAF. The more sterically accessible alkene (A ring) was then hydrogenated under palladium catalysis. Oxidation with TPAP/NMO[32] afforded cyclopentanone **25** in high yield for the sequence. Formation of the requisite vinyl triflate proceeded smoothly. To our delight, coupling between the vinyl triflate and *i*-PrMgCl proceeded to give triene **26** in high yield, using catalytic conditions reported by Bäckvall and co-workers.[33]

Installing oxygenation on the A ring from compound **26**, once again proved taxing. All attempts to isomerize the C12-C13 double bond failed. Preliminary molecular modeling suggested that the tricyclic ring system adopted a twisted structure, which does not allow for efficient conjugation in the desired triene. Consequently, the trisubsubstituted A ring alkene is more thermodynamically favored.

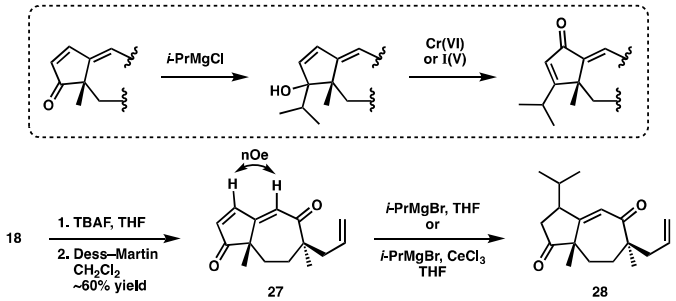
Scheme 10.



In a final attempt to functionalize the A ring, we planned to employ a Grignard addition/oxidative transposition[34,35] sequence (Scheme 11, box) in order to install the C12 isopropyl and C14 ketone. Our prospects were bolstered by precedent from the Phillips[36] and Mander[37] labs, who performed an analogous transformation with cyclopentenones. This approach was evaluated by first converting silyl ether **18** into cyclopentenone **27**. Performing nOe experiments on compound **27** confirmed the site of A-ring oxidation. Treating ketone **27** with *i*-PrMgBr provided a product, whose ^{1}H NMR spectrum was deficient by two alkene protons. This was tentatively assigned as conjugate

addition product **28**. A similar result was obtained when the Grignard addition was performed in the presence of $CeCl_3$.[38] After our work was completed, Wicha and co-workers successfully performed a similar 1,2-addition/oxidative transposition en route to the A ring of guacastepene.[7h,39] Notably, their bicyclic intermediate contained a trans ring fusion between the A and B rings. This likely enforces a different conformation that provides a more open approach to the C12 ketone.

Scheme 11.



3. Conclusion

We have developed the first catalytic enantioselective route to the tricyclic core common to the guanacastepene and heptemerone diterpenoids. Our route relies on sequential Pd-catalyzed decarboxylative allylic alkylation reactions to generate the two all carbon quaternary stereocenters with high fidelity. We have also identified conditions through which oxygenation and the C12 isopropyl group can be introduced to the A ring. Although there is still work to be done, particularly on the A ring, the advanced intermediates we have generated may yet prove useful; especially when one considers the potential utility of biocatalysis as a means to perform regioselective C–H oxidation reactions.[40]

4. Experimental section

Unless otherwise stated, reactions were performed in flame-dried glassware under an Ar or N_2 atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Triethylamine, pyridine, and diisopropylamine were distilled from calcium hydride immediately prior to use. Isobutanol was distilled from CaO prior to use. β-bromostyrene was distilled (110 ºC, 20 mmHg) and storred under Ar in a Schlenk flask. Allyl cyanoformate,[41] TBSOTf,[42] and Ru[(*S*,*S*)-Ts-DPEN](*p*-cymene)[28a] were prepared by known methods. (*S*)- and (*R*)-*t*-Bu-PHOX was prepared by known methods.[43] (*R*)-*t*-Leucinol was resolved using a known procedure.[44] Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, anisaldehyde, or $KMnO_4$ staining. ICN Silica gel (particle size 0.032-0.063 mm) was used for flash chromatography. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing chiralcel AD, OD-H, or OJ columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd with visualization at 254 nm. Analytical achiral GC was performed with an Agilent 6850 GC utilizing a DB-WAX (30m x 0.25 mm) column (1.0 mL/min carrier gas flow). Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz respectively) or Varian Unity Inova 500 (at 500 MHz and 125 MHz respectively), and are reported relative to $CDCl_3$/$CHCl_3$ (^{1}H NMR δ 7.26, ^{13}C NMR δ 77.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). The following abbreviations are used to report NMR data: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, br = broad, obsc = obscured, app = apparent. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the Caltech Mass Spectral Facility.

4.1. 3-Isobutoxycyclohept-2-enone (7)

A 250 mL round-bottom flask fixed with a Dean–Stark trap was charged with 1,3-cycloheptanedione (**6**, 5.0054 g, 39.7 mmol) and toluene (40 mL). Isobutanol (30 mL, 325 mmol, 8.2 equiv) and PPTS (149.6 mg, 0.595 mmol, 1.5 mol%) were added and the mixture was then placed in an oil bath pre-heated to 130 °C. After two hours TLC indicated complete consumption of starting material. The reaction was cooled and concentrated *in vacuo*. The residue was then distilled at 0.6 mmHg, collecting the portion that distilled at 91–96 °C, to afford the title compound (5.3025 g, 73% yield) as a yellow oil. R_F = 0.06 (10:1 Hexane:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.37 (s, 1H), 3.49 (d, *J* = 6.6 Hz, 2H), 2.60-2.56 (m, 4H), 2.00 (app sept, *J* = 6.6 Hz, 1H), 1.88-1.77 (m, 4H), 0.96 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.5, 176.6, 106.0, 75.0, 41.9, 33.1, 27.9, 23.7, 21.5, 19.3; IR (Neat Film NaCl) 2958, 2872, 1646, 1607, 1469, 1237, 1190, 1174 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{18}O_2$ $[M]^{+\bullet}$: 182.1307; found 182.1310.

4.2. Allyl 4-isobutoxy-1-methyl-2-oxocyclohept-3-enecarboxylate (5)

n-Butyllithium (2.12 M in hexane, 15 mL, 31.8 mmol) was added to a solution of *N*,*N*-diisopropylamine (4.4 mL, 31.4 mmol) in 100 mL THF at –78 °C and the solution stirred for 30 min. A solution of 3-isobutoxycyclohept-2-enone (**7**, 4.9996 g, 27.43 mmol) in 10 mL THF was added via cannula with a 5 mL THF rinse. After stirring for 30 min, allyl cyanoformate (3.3677 g, 30.3 mmol) was added. The reaction was kept at –78 °C for 3 hours and then quenched with 50 mL of half saturated aq. NH_4Cl and allowed to thaw. The mixture was diluted with 50 mL Et_2O and the aqueous layer washed 3 x 50 mL Et_2O. The combined organic layers were washed sequentially with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was then dissolved in 60 mL THF and cooled to 0 °C. NaH (60% dispersion in mineral oil, 1.2218 g, 30.5 mmol) was added in portions over 10 min. The mixture was stirred cold 20 min, and then MeI (5 mL, 80.3 mmol) was added. The reaction was then heated to 50 °C for 1 hour. The reaction was then quenched by the careful addition of 50 mL of half saturated aq. NH_4Cl. The mixture was diluted with 50 mL Et_2O and the aqueous layer washed 3 x 25 mL Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. Silica gel chromatography (5 x 21 cm, 10:1 hexanes:EtOAc) afforded the title compound as a pale yellow oil (5.9924 g, 78% yield). R_F = 0.20 (10:1 Hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 (dddd, *J* = 5.4, 5.4, 10.5, 16.8 Hz, 1H), 5.40 (s, 1H), 5.29 (dddd, *J* = 1.5, 1.5, 1.5, 17.1 Hz, 1H), 5.20 (dddd, *J* = 1.2, 1.2, 1.2, 10.5 Hz, 1H), 4.63 (dddd, *J* = 1.2, 1.2, 5.7, 13.2 Hz, 1H), 4.56 (dddd, *J* = 1.2, 1.2, 5.1, 12.9 Hz, 1H), 3.51 (dd, *J* = 6.6, 9.6 Hz, 1H), 3.46 (dd, *J* = 6.6, 9.3 Hz, 1H), 2.59 (ddd, *J* = 4.2, 9.3, 18 Hz, 1H), 2.47-2.36 (m, 2H), 2.04-1.92 (obsc m, 1H), 1.98 (app sept, *J* = 6.8 Hz, 1H), 1.81 (ddd, *J* = 4.2, 9.3, 18.9 Hz, 1H), 1.70 (ddd, 4.5, 7.5, 14.4 Hz, 1H), 1.43 (s, 3H), 0.95 (app d, *J* = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8, 173.7, 173.3, 131.7, 118.2, 104.9, 74.6, 65.5, 58.8, 34.1, 33.7, 27.7, 24.0, 21.1, 19.0; IR (Neat Film NaCl) 3084, 2959, 2935, 1733, 1652, 1612,

1456, 1383, 1233, 1197, 1170, 1114, 994 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{16}H_{24}O_4$ $[M]^{+\cdot}$: 280.1675; found 280.1686.

*4.3. (R)-7-Allyl-3-isobutoxy-7-methylcyclohept-2-enone ((R)-**4**)*

In a nitrogen filled glove box, a flask was charged with Pd(dm-dba)$_2$ (568.4 mg, 0.697 mmol, 2 mol%), (*R*)-*t*Bu-PHOX (334.8 mg, 0.864 mmol, 2.5 mol%), and 200 mL toluene. The mixture was stirred 30 min, at which time allyl 4-isobutoxy-1-methyl-2-oxocyclohept-3-enecarboxylate (**5**, 9.8032 g, 34.97 mmol) was added with a total of 150 mL toluene. The reaction was then taken out of the govebox, placed under a stream of argon, and stirred 60 hrs. The mixture was then evaporated *in vacuo*. Silica gel chromatography (5 x 18 cm, 25:1 hexanes:EtOAc) afforded the title compound as a colorless oil (7.8401 g, 95% yield). R_F = 0.36 (10:1 Hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 (dddd, *J* = 7.2, 7.2, 10.8, 15.9 Hz, 1H), 5.31 (s, 1H), 5.05 (br s, 1H), 5.01 (dddd, *J* = 1.5, 1.5, 2.7, 5.1 Hz, 1H), 3.51 (dd, *J* = 6.6, 9.3 Hz, 1H), 3.45 (dd, *J* = 6.6, 9.3 Hz, 1H), 2.50-2.45 (m, 2H), 2.38 (app dd, *J* = 7.2, 13.5 Hz, 1H), 2.20 (dddd, *J* = 1.2, 1.2, 7.5, 8.7 Hz, 1H), 1.98 (app sept, *J* = 6.6 Hz, 1H), 1.89-1.70 (m, 3H), 1.63-1.55 (m, 1H), 1.14 (s, 3H), 0.95 (app d, *J* = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.5, 171.1, 134.4, 117.7, 104.8, 74.3, 51.3, 45.2, 35.9, 35.0, 27.8, 25.0, 19.7, 19.1; IR (Neat Film NaCl) 3075, 2959, 2932, 1614, 1470, 1387, 1213, 1192, 1172, 998, 912 cm^{-1}; HRMS *m/z* calc'd for $C_{15}H_{24}O_2$ $[M]^+$: 236.1776, found 236.1775; $[\alpha]_D^{24.9}$ +61.39 (*c* 1.055, CH_2Cl_2, 87% ee).

*4.4. (R)-4-Allyl-4-methyl-3-styrylcyclohept-2-enone ((R)-**3**)*

β-Bromostyrene (7 mL, 54.57 mmol) was dissolved in 64 mL Et_2O and cooled to –78 °C. *t*-BuLi (1.6 M in pentane, 64 mL, 102.4 mmol) was added over 40 min. The mixture was stirred at –78 °C for 1 hr, at which time (*R*)-7-allyl-3-isobutoxy-7-methylcyclohept-2-enone (**4**, 7.8335 g, 33.14 mmol) in 15 mL Et_2O was added by cannula with a 5 mL rinse. After 90 min, the reaction was warmed with an ice bath and stirred for 1 hr. The reaction was quenched with 10% HCl (100 mL), and the volatiles removed *in vacuo*. To the residue was added 100 mL THF. The mixture was then heated to 50 °C for 12 hrs. After cooling to room temperature, the mixture was extracted 4 x 100 mL Et_2O. The combined organic extracts were dried over $MgSO_4$, and evaporated *in vacuo*. Silica gel chromatography (5 x 17 cm, ~700 mL 20:1 hexanes:EtOAc then ~1.6 L 15:1 hexanes:EtOAc) afforded the title compound as a viscous yellow oil (8.0542 g, 91% yield). R_F = 0.23 (10:1 Hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.27 (m, 5H), 6.90 (s, 2H), 6.31 (s, 1H), 5.68 (dddd, *J* = 6.6, 8.1, 10.5, 17.1 Hz, 1H), 5.09-5.01 (m, 2H), 2.66-2.61 (m, 2H), 2.47 (dd, *J* = 6.6, 14.1 Hz, 1H), 2.14 (dd, *J* = 8.1, 14.1 Hz, 1H), 1.93-1.80 (m, 3H), 1.70-1.60 (m, 1H), 1.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.5, 158.3, 136.5, 133.7, 133.1, 129.0, 128.7, 128.3, 126.9, 126.9, 118.3, 46.0, 44.3, 44.2, 38.5, 26.6, 17.4; IR (Neat Film NaCl) 3075, 3026, 2925, 1640, 1582, 1450, 1344, 1250, 1217, 963, 916, 752, 694 cm^{-1}; HRMS *m/z* calc'd for $C_{19}H_{22}O$ $[M]^+$: 266.1671, found 266.1668; $[\alpha]_D^{24.8}$ +33.70 (*c* 1.19, $CHCl_3$, 88% ee).

*4.5. (±)-8a-methyl-6,7,8,8a-tetrahydroazulen-5(1H)-one (**8**)*

To a solution of (±)-4-allyl-4-methyl-3-styrylcyclohept-2-enone (**3**, 634.g mg, 2.38 mmol) in 80 mL degassed (argon bubbling) CH_2Cl_2 was added the second generation Grubbs catalyst (5.2 mg, 0.00612 mmol, 0.25 mol%). The mixture was then heated to 50 ºC for 50 min and then cooled to ambient temperature. Ethyl vinyl ether (5 mL) was added and the mixture stirred 30 min. Evaporation *in vacuo*, followed by silica gel chromatography (2 cm x 16 cm, 15:1 hexane:EtOAc) afforded the title compound as a colorless oil (351.3 mg, 91% yield). R_F = 0.17 (10:1 Hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.34 (ddd, *J* = 0.6, 3, 5.4 Hz, 1H), 6.14 (ddd, 1.5, 2.1, 5.4 Hz, 1H), 5.87 (s, 1H), 2.71 (ddddd, *J* = 0.9, 0.9, 3.6, 6.3, 15 Hz, 1H), 2.59-2.49 (m, 2H), 2.41 (ddd, *J* = 1.5, 2.7, 18 Hz, 1H), 2.14-1.80 (m, 4H), 1.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.6, 169.0, 142.6, 134.2, 121.5, 51.4, 46.5, 44.9, 37.7, 29.5, 21.0; IR (Neat Film NaCl) 3059, 2930, 1650, 1615, 1449, 1352, 1261, 968 cm^{-1}; HRMS *m/z* calc'd for $C_{11}H_{14}O$ $[M]^+$: 162.1045, found 162.1040.

*4.6. (±)-(6R,8aR)-6-Allyl-6,8a-dimethyl-6,7,8,8a-tetrahydroazulen-5(1H)-one (syn-**2**)*

To s solution of (±)-8a-methyl-6,7,8,8a-tetrahydroazulen-5(1*H*)-one (**8**, 132.9 mg, 0.819 mmol) in 5 mL THF cooled to –78 °C was added a solution of LHMDS (1.0M in THF, 0.9 mL, 0.9 mmol). The mixture was stirred 30 min and then allyl cyanoformate (106 mg, 0.954 mmol) was added. After 30 min, 8 mL 50% sat. NH_4Cl was added and the mixture allowed to warm to ambient temperature. The aqueous layer was extracted with 3 x 10 mL Et_2O, and the combined organic layers dried with $MgSO_4$ and evaporated *in vacuo*. The crude residue was then dissolved in 5 mL THF and cooled to 0 °C. NaH (60% dispersion in mineral oil, 34.8 mg, 0.87 mmol) was added and the mixture stirred 10 min. MeI (140 □L, 2.25 mmol) was added and the reaction warmed to ambient temperature. After 1 hour, the reaction was quenched by the careful addition of ~5 mL 10% HCl. The mixture was then diluted with 10 mL H_2O and 10 mL Et_2O. The aqueous layer was awashed 3 x 10 mL Et_2O. The combined organic layers were dried with $MgSO_4$ and evaporated *in vacuo*. Flash chromatography (2 x 14 cm, 10:1 Hex/EtOAc) afforded β-ketoester **9** (213.3 mg, 74% yield, 1 diastereomer) as a yellow oil. R_F = 0.36 (5:1 Hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.38 (ddd, *J* = 2.7, 2.7, 5.4 Hz, 1H), 6.15-6.10 (m, 1H), 5.95 (dddd, *J* = 5.4, 5.4, 10.8, 16.8 Hz, 1H), 5.76 (s, 1H), 5.34 (dddd, *J* = 1.5, 1.5, 1.5, 17.4 Hz, 1H), 5.22 (dddd, *J* = 1.5, 1.5, 1.5, 10.5 Hz, 1H), 4.74-4.62 (m, 2H), 2.81 (ddd, *J* = 2.7, 14.7, 14.7 Hz, 1H), 2.55 (bd, *J* = 18 Hz, 1H), 2.41 (ddd, *J* = 1.5, 3, 18 Hz, 1H), 2.11 (ddd, *J* = 2.1, 14.1, 14.1 Hz, 1H), 1.81 (ddd, *J* = 2.7, 6, 14.7 Hz, 1H), 1.70 (ddd, *J* = 1.8, 5.7, 14.4 Hz, 1H), 1.48 (s, 3H), 1.25 (s, 3H).

A flame-dried vial was charged with Pd(dm-dba)$_2$ (4.5 mg, 0.0.00552 mmol, 5 mol%), (*S*)-*t*Bu-PHOX (2.5 mg, 0.00645 mmol, 5.8 mol%), and 3 mL THF. The mixture is stirred at 25 °C for 30 min at which time β-ketoester **9** (29 mg, 0.111 mmol) prepared above was added by syringe. The reaction was stirred at 25 °C for 5.5 hrs. Evaporation *in vacuo* followed by silica gel chromatography (3 x 3 cm, 20:1 hexanes:EtOAc) afforded the title compound as a light yellow oil (20.8 mg, 86% yield, >10:1 mixture of diastereomers). R_F = 0.40 (10:1 Hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) **Major diastereomer:** δ 6.26 (ddd, *J* = 3, 3, 5 Hz, 1H), 6.09 (ddd, *J* = 1.8, 1.8, 5.4 Hz, 1H), 5.71 (s, 1H), 5.61 (dddd, *J* = 6.9, 7.5, 10.2, 18 Hz, 1H), 5.06-4.97 (m, 2H), 2.55-2.41 (m, 2H), 2.35 (ddd, *J* = 1.8, 2.7, 18 Hz, 1H), 2.26-1.93 (m, 3H), 1.70 (app d, *J* = 5.1 Hz, 1H), 1.64 (app d, *J* = 5.7 Hz, 1H), 1.12 (s, 3H), 1.07 (s, 3H); **Diagnostic peaks of minor diastereomer:** δ 5.74 (s), 1.15 (s), 1.11 (s); ^{13}C NMR (75 MHz, CDCl3) □ 208.9, 164.5, 141.4, 133.6, 133.3, 119.5, 118.0, 50.9, 50.7, 45.2, 42.2, 34.1, 33.2, 28.8, 23.4; IR (Neat Film NaCl) 3075, 3059, 2961, 2929, 1656, 1625, 1450, 1375, 1220, 1204, 1122, 913 cm^{-1}.

*4.7. (5R)-Allyl 5-allyl-1,5-dimethyl-2-oxo-4-styrylcyclohept-3-enecarboxylate (**10**)*

To a solution of hexamethyldisilazane (10 mL, 47.71 mmol) in 155 mL THF at –78 °C, was added n-butyllithium (2.4 M in hexane, 19 mL, 45.6 mmol) over 5 min. The mixture was stirred

30 min and then (*R*)-4-allyl-4-methyl-3-styrylcyclohept-2-enone (**3**, 8.0542 g, 30.24 mmol) in 15 mL THF (precooled to –78 °C) was added via cannula with a 5 mL rinse. After 30 min, allyl cyanoformate (4.4772 g, 40.30 mmol) was added quickly. After 10 min, 100 mL of half saturated aq. NH_4Cl was added to the cold reaction. The layers were separated and the aqueous layer washed with 3 x 100 mL EtOAc. The combined organic layers were dried with $MgSO_4$ and evaporated *in vacuo*. The residue was then dissolved in 60 mL CH_3CN, and Cs_2CO_3 (14.68 g, 45.06 mmol) and MeI (10 mL, 160.28 mmol) were added. The mixture was then heated to 80 °C. After 4 hrs and 20 min the reaction was cooled to room temperature and filtered through a plug of silica gel (5 x 1 cm) which was then rinsed with 3 x 50 mL EtOAc. The filtrate was then evaporated *in vacuo*. Silica gel chromatography (5 x 17 cm, 20:1 hexanes:EtOAc) afforded the title compound as an orange-yellow oil (9.9142 g, 90% yield). ^{1}H NMR indicated an ~ 3:1 mixture of diasteromers. R_F = 0.26 (10:1 Hexane:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) **Major diastereomer:** δ 7.44-7.41 (m, 2H), 7.37-7.33 (m, 2H), 7.30-7.26 (m, 1H), 6.91 (d, *J* = 15.5 Hz, 1H), 6.85 (d, *J* = 15.5 Hz, 1H), 6.28 (s, 1H), 5.90 (dddd, *J* = 5.5, 5.5, 11, 22.5 Hz, 1H), 5.68 (dddd, *J* = 7.5, 7.5, 10.5, 17.5 Hz, 1H), 5.33 (dddd, *J* = 1.5, 1.5, 1.5, 17.5 Hz, 1H), 5.26-5.21 (m, 1H), 5.09-5.03 (m, 2H), 4.70-4.56 (m, *2*H), 2.44 (dd, *J* = 7.5, 14.5 Hz, 1H), 2.24 (app dd, *J* = 8.5, 15 Hz, 1H), 2.18-2.13 (m, 2H), 1.80 (dd, *J* = 9.5 14 Hz, 1H), 1.54 (dd, *J* = 8.5 Hz, 15 Hz, 1H), 1.44 (s, 3H), 1.23 (s, 3H), **Minor diastereomer:** δ 7.44-7.41 (m, 2H), 7.37-7.33 (m, 2H), 7.30-7.26 (m, 1H), 6.89 (d, *J* = 16 Hz, 1H), 6.82 (d, *J* = 15.5 Hz, 1H), 6.31 (s, 1H), 5.89 (dddd, *J* = 5.5, 5.5, 11.5, 22.5 Hz, 1H), 5.61 (dddd, *J* = 7, 8.5, 10.5, 17 Hz, 1H), 5.31 (*J* = 1.5, 1.5, 1.5, 17 Hz, 1H), 5.26-5.21 (m, 1H), 5.06-4.99 (m, 2H), 4.70-4.56 (m, *2*H), 2.41-2.34 (obsc m, 1H), 2.11 (obsc dd, *J* = 8, 14 Hz, 1H), 1.79 (obsc ddd, 2H), 1.66 (ddd, *J* = 1, 9, 10 Hz, 2H), 1.47 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) **Major diastereomer:** δ 202.6, 173.1, 156.9, 136.5, 133.5, 133.3, 131.8, 128.7, 128.4, 128.1, 126.9, 124.6, 118.4, 118.0, 65.6, 60.2, 44.9, 44.5, 34.5, 29.3, 26.3, 23.4, **Minor diastereomer:** δ 202.2, 172.8, 154.9, 136.5, 133.4, 133.1, 131.7, 128.7, 128.3, 128.0, 126.8, 125,2, 118.4, 118.2, 65.7, 59.8, 46.1, 44.3, 34.1, 28.9, 25.5, 21.8, ; IR (Neat Film NaCl) 3078, 3025, 2974, 2934, 1735, 1653, 1648, 1584, 1448, 1375, 1221, 1196, 1103, 965, 918 cm^{-1}; FAB$^+$ HRMS *m/z* calc'd for $C_{24}H_{29}O_3$ $[M+H]^+$: 365.2117, found 365.2117.

*4.8. (4R,7R)-4,7-Diallyl-4,7-dimethyl-3-styrylcyclohept-2-enone (anti-**11**)*

In a nitrogen filled glove box, a flask was charged with Pd(dm-dba)$_2$ (440.2 mg, 0.540 mmol, 2 mol%) and (*R*)-*t*Bu-PHOX (253.0 mg, 0.653 mmol, 2.4 mol%) and 2500 mL THF. The mixture is stirred 30 min, at which time (5*R*)-allyl 5-allyl-1,5-dimethyl-2-oxo-4-styrylcyclohept-3-enecarboxylate (**10**, 9.9052 g, 27.18 mmol) was added with a total of 50 mL THF. The reaction was taken out of the glovebox and stirred at 25 °C for 24 hrs. Evaporation *in vacuo* followed by silica gel chromatography (5 x 17 cm, 25:1 hexanes:EtOAc) afforded the title compound as a light yellow oil (8.163 g, 94% yield, 10:1 mixture of diastereomers). R_F = 0.52 (10:1 Hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) **Major diastereomer:** δ 7.45-7.27 (m, 5H), 6.90 (d, *J* = 15.3 Hz, 1H), 6.82 (d, *J* = 15.6 Hz, 1H), 6.19 (s, 1H), 5.79-5.54 (m, 2H), 5.08-4.97 (m, 4H), 2.34 (app dd, *J* = 6.3, 14.1 Hz, 1H), 2.24 (app dd, *J* = 6.9, 12.9 Hz, 1H), 2.16 (app dd, *J* = 8.1, 14.1 Hz, 1H), 2.08 (app dd, *J* = 8.1, 13.8 Hz, 1H), 1.93-1.84 (m, 1H), 1.75-1.66 (m, 1H), 1.56-1.45 (m, 2H), 1.25 (s, 3H), 1.16 (s, 3H); **Diagnostic peaks of minor diastereomer:** δ 6.20 (s), 1.20 (s), 1.11 (s); 13C NMR (75 MHz, CDCl3) □ 209.4, 154.8, 136.7, 133.7, 133.7, 132.8, 128.7, 128.3, 128.2, 126.8, 125.2, 118.1, 118.0, 52.9, 46.2, 45.3, 44.4, 34.3, 29.8, 25.6, 22.8; IR (Neat Film NaCl) 3076, 3027, 2967, 2931, 1659, 1587, 1449, 1373, 1194, 1147, 1120, 962, 915, 753, 694 cm^{-1}; FAB$^+$ HRMS *m/z* calc'd for $C_{23}H_{29}O$ $[M+H]^+$: 321.2218, found 321.2225; $[\alpha]_D^{24.6}$ +87.18 (*c* 1.27, $CHCl_3$, 10:1 dr, anti-Me diastereomer 97% ee).

*4.9. (6R,8aR)-6-Allyl-6,8a-dimethyl-6,7,8,8a-tetrahydroazulen-5(1H)-one (anti-**2**)*

A 3000 mL flask was charged with (4*R*,7*R*)-4,7-diallyl-4,7-dimethyl-3-styrylcyclohept-2-enone (**11**, 8.1630 g, 25.47 mmol) and 2000 mL CH_2Cl_2. Argon was bubbled through the solution using a glass gas dispersion tube for 20 min, at which time ethylene was bubbled through the mixture for 5 min. The second generation Grubbs catalyst (434.1 mg, 0.511 mmol, 2 mol%) was added and ethylene was bubbled through the mixture for 15 min, followed by flushing the headspace for 15 min. The flask was then sealed. After 17 hrs, a second portion of the second generation Grubbs catalyst (112.7 mg, 0.133 mmol, 0.5 mol%) was added. After 3 hrs, the reaction was quenched by adding 90 mL ethyl vinyl ether and allowed to stir 1.5 hrs. Evaporation *in vacuo*, followed by silica gel chromatography (5 cm x 17 cm, 4% Et_2O in hexane) afforded the title compound as a yellow oil (5.3386 g, 89% yield with 6% starting material). R_F = 0.40 (10:1 Hexane:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) **Major diastereomer:** δ 6.28 (ddd, *J* = 3, 3, 5 Hz, 1H), 6.10-6.08 (m, 1H), 5.83 (dddd, *J* = 6.5, 7.5, 11, 16 Hz, 1H), 5.73 (s, 1H), 5.06-5.04 (m, 1H), 5.04-5.00 (m, 1H), 2.53-2.46 (m, 2H), 2.35 (ddd, *J* = 1.5, 3, 18 Hz, 1H), 2.15 (app dd, *J* = 8, 13.5 Hz, 1H), 2.13-2.06 (m, 2H), 1.76-1.67 (m, 1H), 1.55-1.47 (m, 1H), 1.15 (s, 3H), 1.11 (s, 3H); **Diagnostic peaks of minor diastereomer:** δ 5.71 (s), 1.12 (s), 1.07 (s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.5, 165.3, 141.7, 135.7, 133.8, 119.9, 117.4, 50.6, 50.0, 45.4, 44.2, 33.3, 32.7, 28.8, 24.7; IR (Neat Film NaCl) 3072, 2966, 2914, 1648, 1625, 1448, 1378, 1225, 1122, 1079, 912 cm^{-1}; HRMS *m/z* calc'd for $C_{15}H_{20}O$ $[M]^+$: 216.1514, found 216.1505; $[\alpha]_D^{24.9}$ +12.59 (*c* 1.165, $CHCl_3$).

*4.10. (1R,6R,8aS,Z)-6-allyl-1-hydroxy-6,8a-dimethyl-6,7,8,8a-tetrahydroazulen-5(1H)-one (**17**)*

A flask was charged with (6*R*,8a*R*)-6-allyl-6,8a-dimethyl-6,7,8,8a-tetrahydroazulen-5(1*H*)-one (**2**, 4.4093 g, 20.38 mmol) and 60 mL CH_2Cl_2. To the ice cooled mixture was added Et_3N (12 mL, 86.10 mmol) followed by TBSOTf (9.5 mL, 41.36 mmol) over 10 min. The reaction was stirred cold for 10 min and then allowed to warm to ambient temperature. After 3 hrs the reaction was cooled with an ice bath and 50 mL sat. $NaHCO_3$ was added. The mixture was extracted with hexane (3 x 50 mL) and the combined organic layers dried with Na_2SO_4. Evaporation *in vacuo* afforded a yellow residue that was dissolved in 100 mL 95% EtOH and cooled with an ice bath. MMPP (12.6 g, 80%, 20.38 mmol) was added in portions over 1 hour. After stirring a further 15 min the mixture was evaporated *in vacuo* to a volume of 20-30 mL. Water (100 mL) was added and the mixture extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried with $MgSO_4$ and evaporated *in vacuo*. Silica gel chromatography (3 cm x 18 cm, ~330 mL 5:1 Hex/EtOAc, then ~600 mL 3:1 Hex/EtOAc) afforded the title compound as a pale yellow oil (3.9786 g, 84% yield). R_F = 0.10 (5:1 Hexane:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.35 (dd, *J* = 2, 5.5 Hz, 1H), 6.31 (d, *J* = 5 Hz, 1H), 5.83 (dddd, *J* = 7, 8, 11.5, 11.5 Hz, 1H), 5.82 (s, 1H), 5.07-5.03 (m, 2H), 4.24 (d, *J* = 2.5 Hz, 1H), 2.49 (dd, *J* = 6.5, 14 Hz, 1H), 2.29 (m, 1H), 2.20 (dd, *J* = 8, 14 Hz, 1H), 2.10 (m, 1H), 1.93 (br s, 1H), 1.64 (app ddd, *J* = 2, 6.5, 6.5 Hz, 1H), 1.60 (app ddd, *J* = 2, 6, 6 Hz, 1H), 1.15 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.1, 161.6,

141.1, 137.4, 135.4, 122.6, 117.6, 84.8, 49.7, 48.1, 43.8, 30.9, 27.6, 27.1, 24.4; IR (Neat Film NaCl) 3401, 3073, 2963, 2915, 1631, 1450, 1226, 1089, 1037, 915, 861 cm^{-1}; HRMS *m/z* calc'd for $C_{15}H_{20}O_2$ $[M]^+$: 232.1463, found 232.1467; $[\alpha]_D^{23.1}$ –64.33 (*c* 1.49, $CHCl_3$).

*4.11. (1R,6R,8aS)-6-Allyl-1-(tert-butyldimethylsilyloxy)-6,8a-dimethyl-6,7,8,8a-tetrahydroazulen-5(1H)-one (**18**)*

A solution of (1*R*,6*R*,8a*S*,*Z*)-6-allyl-1-hydroxy-6,8a-dimethyl-6,7,8,8a-tetrahydroazulen-5(1*H*)-one (**17**, 3.9786 g, 17.13 mmol) in 84 mL CH_2Cl_2 was cooled to –78 °C. To this mixture was added 2,6-lutidine (8 mL, 68.68 mmol, 4 equiv.), followed by TBSOTf (5.9 mL, 25.69 mmol, 1.5 equiv.) over ~5 min. The reaction was stirred cold for 45 min and then quenched by adding 100 mL sat. $NaHCO_3$. The mixture was allowed to thaw and the layers separated. The aqueous layer was washed with EtOAc (3 x 100 mL) and the combined organic layers dried with $MgSO_4$. Evaporation *in vacuo*, followed by silica gel chromatography (5 cm x 15 cm, 35:1 pet. ether:EtOAc) afforded the title compound as a colorless oil (4.5484 g, 77% yield). R_F = 0.17 (20:1 Hexane:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.23 (d, *J* = 5.5 Hz, 1H), 6.19 (dd, *J* = 2.5, 5 Hz, 1H), 5.84 (dddd, *J* = 7, 8, 12.5, 12.5 Hz, 1H), 5.78 (s, 1H), 5.06-5.01 (m, 2H), 4.23 (d, *J* = 2.5 Hz, 1H), 2.48 (dd, *J* = 7, 13.5 Hz, 1H), 2.31 (ddd, *J* = 2.5, 14.5, 14.5 Hz, 1H), 2.20 (dd, *J* = 8, 14 Hz, 1H), 2.04 (ddd, *J* = 2, 15, 15 Hz, 1H), 1.59 (ddd, *J* = 2, 5.5, 14.5 Hz, 1H), 1.46 (ddd, *J* = 2, 5.5, 14.5 Hz, 1H), 1.15 (s, 3H), 1.06 (s, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.3, 162.4, 141.6, 136.2, 135.6, 122.0, 117.4, 85.1, 49.7, 48.4, 43.8, 31.0, 27.9, 27.6, 25.8, 24.4, 18.3, –4.3, –4.7; IR (Neat Film NaCl) 3073, 2957, 2929, 1656, 1637, 1472, 1258, 1096, 1067, 872, 837, 775 cm^{-1}; HRMS *m/z* calc'd for $C_{21}H_{34}O_2Si$ $[M]^+$: 346.2328, found 346.2326; $[\alpha]_D^{23.1}$ –149.36 (*c* 1.56, $CHCl_3$).

*4.12. (6R,8aS)-6-Allyl-6,8a-dimethyl-6,7,8,8a-tetrahydroazulene-1,5-dione (**27**)*

A vial was charged with a mixture of (1*R*,6*R*,8a*S*)-6-allyl-1-(*tert*-butyldimethylsilyloxy)-6,8a-dimethyl-6,7,8,8a-tetrahydroazulen-5(1*H*)-one and (6*R*,8a*R*)-6-allyl-6,8a-dimethyl-6,7,8,8a-tetrahydroazulen-5(1*H*)-one (20.3 mg) and 0.3 mL THF. TBAF (1.0M in THF, 50 μL, 0.050 mmol) was added and the mixture stirred 15 min. The volatiles were removed *in vacuo* and the residue taken up in EtOAc and filtered through a plug of silica gel, rinsing with EtOAc. Evaporation *in vacuo* gave a residue that was dissolved in 0.3 mL CH_2Cl_2. Dess–Martin periodinane (19.6 mg, 0.0462 mmol) was added. After 40 min, isopropanol was added and the mixture evaporated *in vacuo*. Flash chromatography (0.7 cm x 7 cm, 10:1 Hex/EtOAc) afforded the title compound as a colorless oil (8 mg): R_F = 0.11 (10:1 Hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 5.7 Hz, 1H), 6.37 (d, *J* = 5.4 Hz, 1H), 6.00 (s, 1H), 5.83 (dddd, *J* = 7.2, 7.2, 10.5, 14.7 Hz, 1H), 5.12-5.02 (m, 2H), 2.40 (app dd, *J* = 7.2, 14.1 Hz, 1H), 2.29 (app dd, *J* = 7.2, 13.5 Hz, 1H), 2.05 (ddd, *J* = 2.4, 14.7, 14.7 Hz, 1H), 1.92 (ddd, *J* = 3.3, 5.1, 14.7 Hz, 1H), 1.77 (obsc ddd, *J* = 2.4, 18.3 Hz, 1H), 1.67 (ddd, *J* = 2.7, 5.1, 14.7 Hz, 1H), 1.13 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.4, 207.8, 155.8, 152.8, 134.7, 134.1, 125.2, 118.2, 50.8, 48.9, 43.3, 32.2, 26.8, 22.6, 22.0; IR (Neat Film NaCl) 3071, 2973, 2932, 1713, 1675, 1550, 1448, 1379, 1345, 1227, 1090, 1073, 917, 866, 627 cm^{-1}; HRMS *m/z* calc'd for $C_{15}H_{18}O_2$ $[M]^+$: 230.1307, found 230.1302; $[\alpha]_D^{23.5}$ +46.28 (*c* 0.40, CH_2Cl_2).

*4.13. 3-((1R,6R,8aS,Z)-1-(tert-Butyldimethylsilyloxy)-6,8a-dimethyl-5-oxo-1,5,6,7,8,8a-hexahydroazulen-6-yl)propanal (**19**)*

To a solution of (1*R*,6*R*,8a*S*)-6-allyl-1-(*tert*-butyldimethylsilyloxy)-6,8a-dimethyl-6,7,8,8a-tetrahydroazulen-5(1*H*)-one (**18**, 4.5484 g, 13.12 mmol) in 130 mL degassed CH_2Cl_2 was added 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane[20] (10.3126 g, 66.96 mmol, 5 equiv.) followed by the second generation Hoveyda–Grubbs catalyst (412.5 mg, 0.658 mmol, 5 mol%). The mixture was then heated to reflux for 12 hrs at which time it was cooled and 10 mL ethyl vinyl ether was added. After stirring for 30 min at ambient temperature, the reaction mixture was then concentrated *in vacuo*. The residue was applied to the top of a 6.5 x 1.5 cm pad of silica gel and eluted with a total of 600 mL 10:1 Hex/EtOAc. The filtrate was evaporated *in vacuo* and the residue dissolved in 130 mL THF. Anhydrous Me_3NO[21] (5.03 g, 66.97 mmol) was added and the mixture heated to reflux for 10 hrs. To the cooled reaction mixture was added 50 mL H_2O and the mixture was allowed to stir ~15 min. Brine (50 mL) was added and the layers separated. The organic layer was washed with 50 mL brine, and the combined aqueous layers washed with EtOAc (3 x 100 mL). The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*. Silica gel chromatography (5 x 15 cm, ~600 mL 7:1 Hex/EtOAc then ~450 mL 6:1 Hex/EtOAc) afforded the title compound (3.7336 g, 78%) as a yellow oil. R_F = 0.3 (5:1 Hexane:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (dd, *J* = 1.5, 1.5 Hz, 1H), 6.22 (d, *J* = 5.5 Hz, 1H), 6.20 (dd, *J* = 2.5, 5.5 Hz, 1H), 5.76 (s, 1H), 4.23 (d, *J* = 2.5 Hz, 1H), 2.53 (m, 1H), 2.47 (m, 1H), 2.36 (ddd, *J* = 2, 14.5, 14.5 Hz, 1H), 2.10 (ddd, *J* = 2.5, 14.5, 14.5 Hz, 1H), 2.02 (ddd, *J* = 6.5, 9.5, 14.5 Hz, 1H), 1.72 (ddd, *J* = 6, 9.5, 14 Hz, 1H), 1.54 (ddd, *J* = 2, 6, 14.5 Hz, 1H), 1.46 (ddd, *J* = 2, 5.5, 14.5 Hz, 1H), 1.17 (s, 3H), 1.06 (s, 3H), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.9, 202.7, 162.6, 141.9, 136.1, 121.8, 85.0, 49.5, 48.3, 39.8, 31.6, 31.2, 27.8, 27.4, 25.8, 24.8, 18.2, –4.3, –4.8; IR (Neat Film NaCl) 3059, 2956, 2928, 1725, 1654, 1636, 1472, 1451, 1382, 1361, 1250, 1095, 1062, 936, 870, 837, 775 cm^{-1}; HRMS *m/z* calc'd for $C_{21}H_{34}O_3Si$ $[M]^+$: 362.2277, found 362.2260; $[\alpha]_D^{23.3}$ –127.87 (*c* 2.305, $CHCl_3$).

*4.14. Ethyl 5-((1R,6R,8aS,Z)-1-(tert-butyldimethylsilyloxy)-6,8a-dimethyl-5-oxo-1,5,6,7,8,8a-hexahydroazulen-6-yl)-3-oxopentanoate (**20**)*

A 250 mL round-bottom flask was charged with 3-((1*R*,6*R*,8a*S*,*Z*)-1-(*tert*-butyldimethylsilyloxy)-6,8a-dimethyl-5-oxo-1,5,6,7,8,8a-hexahydroazulen-6-yl)propanal (**19**, 3.7336 g, 10.30 mmol) and 100 mL CH_2Cl_2. Anhydrous $SnCl_2$ (195.4 mg, 1.031 mmol) was added, followed by ethyl diazoacetate (1.1946 g, 10.47 mmol) over ~ 5 min. The reaction was stirred 1.5 hrs at ambient temperature and a further portion of ethyl diazoacetate (210 μL, 2.00 mmol) was added. After stirring another 1.5 hrs, the reaction was concentrated *in vacuo*, and the residue subjected to silica gel chromatography (3 cm x 31 cm, 7:1 Hex:EtOAc) to afford the title compound as a viscous yellow oil (4.0558 g, 88% yield). R_F = 0.28 (5:1 Hexane:EtOAc); **Major keto tautomer:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.23 (d, *J* = 6 Hz, 1H), 6.20 (dd, *J* = 2.5, 5.5 Hz, 1H), 5.75 (s, 1H), 4.23 (d, *J* = 2.5 Hz, 1H), 4.19 (app q, *J* = 7.5 Hz, 2H), 3.48 (s, 1.6H), 2.64 (m, 1H), 2.62 (m, 1H), 2.36 (ddd, *J* = 2, 14.5, 14.5 Hz, 1H), 2.09 (ddd, *J* = 2, 14.5, 14.5 Hz, 1H), 1.97 (ddd, *J* = 6.5, 8.5, 14 Hz, 1H), 1.71 (ddd, *J* = 6, 9.5, 14 Hz, 1H), 1.54 (ddd, *J* = 2.5, 6, 15 Hz, 1H), 1.46 (ddd, *J* = 2, 6, 15 Hz, 1H), 1.27 (dd, *J* = 7, 7 Hz, 3H), 1.17 (s, 3H), 1.06 (s, 3H), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.0, 203.1, 167.4, 162.5, 141.9, 136.1, 121.9, 85.0, 61.3, 49.5, 49.2, 48.3, 38.9, 33.1, 31.2, 27.8, 27.4, 25.8, 24.8, 18.2, 14.1, –4.3, –4.7; IR (Neat Film NaCl) 3054, 2956, 2929, 1744, 1718, 1653, 1636, 1472, 1449, 1367, 1318, 1258, 1165, 1095, 1071, 936, 869, 837, 802, 775 cm^{-1}; HRMS *m/z*

calc'd for $C_{25}H_{40}O_5Si$ $[M]^+$: 448.2645, found 448.2631; $[\alpha]_D^{23.4}$ – 122.05 (*c* 0.870, $CHCl_3$).

*4.15. Knoevenagel cyclization (preparation of compound **21**)*

To a solution of ethyl 5-((1*R*,6*R*,8a*S*,*Z*)-1-(*tert*-butyldimethylsilyloxy)-6,8a-dimethyl-5-oxo-1,5,6,7,8,8a-hexahydroazulen-6-yl)-3-oxopentanoate (**20**, 2.3213 g, 5.17 mmol, 1 equiv) in 52 mL EtOH was added KF (337.9 mg, 0.280 mmol, 1.1 equiv). The mixture was then heated to 80 °C for 10 hrs, at which time TLC analysis (twice developed in 10:1 Hex/EtOAc) indicated no SM was present. The reaction was then cooled and evaporated *in vacuo*. The residue was directly applied to a column of silica (3 x 22 cm) and eluted with 10:1 Hex/EtOAc. Unclean fractions were chromatographed again (2 x 18 cm silica gel) to afford compound **21** (1.6580 g, 74%) as a yellow oil that solidified on standing. R_F = 0.29 (5:1 Hexane:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.19 (d, *J* = 5.5 Hz, 1H), 6.13 (dd, *J* = 2, 5 Hz, 1H), 6.00 (s, 1H), 4.30 (dq, *J* = 7, 13.5 Hz, 1H), 4.23 (dq, *J* = 7, 13.5 Hz, 1H), 4.22 (obsc d, *J* = 3.5 Hz, 1H), 2.64 (m, 1H), 2.62 (m, 1H), 2.27 (app br t, *J* = 13.5 Hz, 1H), 2.10 (br s, 1H), 2.01 (m, 1H), 1.81 (ddd, *J* = 5.5, 5.5, 11 Hz, 1H), 1.62 (ddd, *J* = 2, 7, 15 Hz, 1H), 1.37 (ddd, *J* = 2, 7, 15.5 Hz, 1H), 1.27 (dd, *J* = 7, 7 Hz, 3H), 1.22 (s, 3H), 1.05 (s, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.2, 167.3, 162.1 (br), 161.4 (br), 140.1, 136.6, 132.6, 117.6 (br), 85.2, 61.0, 48.2, 37.6 (br), 36.5, 33.6, 27.2, 27.1 (br), 25.8, 25.8, 24.6 (br), 18.2, 14.1, –4.3, –4.7; IR (Neat Film NaCl) 3054, 2955, 2928, 1734, 1671, 1617, 1472, 1451, 1367, 1321, 1229, 1136, 1093, 1071, 1031, 872, 836, 774 cm^{-1}; FAB^+ HRMS *m/z* calc'd for $C_{25}H_{39}O_4Si$ $[M+H]^+$: 431.2618, found 431.2614; $[\alpha]_D^{23.4}$ –909.69 (*c* 1.945, $CHCl_3$).

*4.16. Diastereoselective reduction of β-ketoester **21***

A solution of Knoevenagel product **21** (1.6173 g, 3.76 mmol) in 40 mL isopropanol, was degassed by bubbling argon through the mixture for 30 min. Ru[(*S*,*S*)-Ts-DPEN](*p*-cymene) (112.9 mg, 0.188 mmol, 5 mol%) was then added. The mixture was stirred at ambient temperature for 24 hrs and then evaporated *in vacuo*. After silica gel chromatography (3 x 24 cm, 7:1 Hex/EtOAc), any fractions containing unreacted starting material were pooled and collected away from the reaction product. This residue (461.8 mg) containing ketoester **21** was then dissolved in 11 mL isopropanol and degassed as above. Ru[(*S*,*S*)-Ts-DPEN](*p*-cymene) (7.2 mg, 0.0120 mmol) was then added. The mixture was stirred at ambient temperature for 36 hrs and then evaporated *in vacuo*. After silica gel chromatography (2 x 17 cm, 7:1 Hex/EtOAc), any fractions containing unreacted starting material were pooled and subjected to one further silica gel column (2 x 17 cm, 7:1 Hex/EtOAc). The final product (**22**) was isolated as a brown viscous oil (1.3934 g, 86%). R_F = 0.26 (5:1 Hexane:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, 50 ºC) δ 6.21 (s, 1H), 6.20 (d, *J* = 5.5 Hz, 1H), 5.95 (dd, *J* = 2.5, 5.5 Hz, 1H), 4.54 (br d, *J* = 3.5 Hz, 1H), 4.24 (dq, *J* = 7, 13.5 Hz, 1H), 4.20 (obsc d, *J* = 2.5 Hz, 1H), 4.19 (dq, *J* = 7, 13.5 Hz, 1H), 2.59 (bs, 1H), 2.12 (app t, *J* = 13 Hz, 1H), 1.95-1.85 (m, 4 H), 1.58 (ddd, *J* = 2, 7.5, 14.5 Hz, 1H), 1.39-1.37 (obsc m, 1H), 1.33 (ddd, *J* = 2, 7.5, 15 Hz, 1H), 1.27 (dd, *J* = 7, 7 Hz, 3H), 1.05 (s, 3H), 1.00 (s, 3H), 0.90 (s, 9H), 0.082 (s, 3H), 0.076 (s, 3H); IR (Neat Film NaCl) 3435, 3054, 2951, 2929, 1700, 1472, 1366, 1257, 1216, 1089, 1073, 873, 835, 773 cm^{-1}; HRMS *m/z* calc'd for $C_{25}H_{40}O_4Si$ $[M]^+$: 432.2696, found 432.2716; $[\alpha]_D^{23.4}$ –707.61 (*c* 0.620, $CHCl_3$). **Note:** due to conformational instability, we were unable to obtain a suitable ^{13}C NMR spectrum.

*4.17. Conversion to acetonide **23***

Ester **22** (1.3934 g, 3.22 mmol) was dissolved in 30 mL THF and cooled to 0 °C. Red-Al (~3.5 M solution in toluene, 3.6 mL, 12.6 mmol) was added slowly over 5 min. The mixture was allowed to stir cold for 1 hr. The reaction was quenched by the careful addition of EtOH (15 mL). The mixture was then warmed to ambient temperature and Na_2SO_4•10 H_2O (15 g) was added. After stirring vigorously for 1 hour, the mixture was filtered through a fritted glass funnel and the salts rinsed with EtOAc(3 x 50 mL). Evaporation *in vacuo* gave a residue that was subjected to flash chromatography (3 x 18 cm, 2:1 Hex/EtOAc) to afford a diol product (960.2 mg, 76% yield). R_F = 0.16 (2:1 Hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.18 (d, *J* = 5.4 Hz, 1H), 5.95 (s, 1H), 5.92 (dd, *J* = 2.1, 5.4 Hz, 1H), 4.40-4.32 (m, *2*H), 4.28-4.20 (m, 2H), 2.40 (bs, 1H), 2.15-1.65 (m, 5H), 1.60 (bs, 1H), 1.55-1.22 (m, 3H), 0.99 (s, 3H), 0.97 (s, 3H), 0.89 (s, 9H), 0.07 (s, 6H); IR (Neat Film NaCl) 3352, 3054, 2953, 2929, 1650, 1472, 1463, 1450, 1362, 1256, 1092, 1059, 1005, 870, 836, 774 cm^{-1}; FAB^+ HRMS *m/z* calc'd for $C_{23}H_{37}O_3Si$ $[(M+H)-H_2]^+$: 389.2512, found 389.2509. **Note:** due to conformational instability, we were unable to obtain a suitable ^{13}C NMR spectrum.

The isolated diol was dissolved in 25 mL CH_2Cl_2 and cooled to 0 °C. PPTS (30.3 mg, 0.121 mmol, 5 mol%) was added, followed by 2,2-dimethoxypropane (6 mL, 48.80 mmol, 20 equiv). After stirring cold for 1 hour, the reaction mixture was evaporated *in vacuo* and the residue subjected to flash chromatography (3 x 25 cm, 25:1 Hex/EtOAc) to afford acetonide **23** (552.8 mg, 52% yield) as a white solid. R_F = 0.32 (20:1 Hexane:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.15 (d, *J* = 5.5 Hz, 1H), 5.88 (dd, *J* = 2.5, 5.5 Hz, 1H), 5.69 (s, 1H), 4.35 (dddd, *J* = 1.5, 3.5, 3.5, 7.5 Hz, 1H), 4.29 (d, *J* = 15.5 Hz, 1H), 4.26 (d, *J* = 2.5 Hz, 1H), 4.13 (ddd, *J* = 2, 2, 16 Hz, 1H), 2.24 (ddd, *J* = 3, 14.5, 14.5 Hz, 1H), 2.00 (ddd, *J* = 3, 14, 14 Hz, 1H), 1.84 (dddd, *J* = 3.5, 3.5, 7, 12.5 Hz, 1H), 1.71 (dddd, *J* = 6, 10.5, 10.5, 10.5 Hz, 1H), 1.60-1.52 (m, 2H), 1.43 (s, 3H), 1.38 (obsc ddd, *J* = 3, 4.5, 13.5 Hz, 1H), 1.35 (s, 3H), 1.29 (ddd, *J* = 3, 5, 15 Hz, 1H), 0.97 (s, 3H), 0.96 (s, 3H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.5, 135.6, 135.5, 134.9, 133.1, 117.8, 99.5, 86.4, 67.8, 60.5, 46.7, 38.6, 36.9, 36.0, 26.9, 25.9, 25.9, 25.3, 25.0, 24.4, 23.8, 18.3, –4.4, –4.7; IR (Neat Film NaCl) 3054, 2951, 2930, 1472, 1378, 1250, 1224, 1092, 1064, 866, 835, 774 cm^{-1}; FAB^+ HRMS *m/z* calc'd for $C_{26}H_{41}O_3Si$ $[(M+H)-H_2]^+$: 429.2825, found 429.2805; $[\alpha]_D^{24.9}$ –514.23 (*c* 1.54, $CHCl_3$).

*4.18. Conversion to pivalate **24***

Compound **23** (30.5 mg, 0.708 mmol) was dissolved in 0.2 mL THF and TBAF (1.0 M in THF, 150 □L, 0.150 mmol) was added at ambient temperature. The reaction was allowed to stir at ambient temperature 2.5 hrs at which time it was filtered through a plug of silica gel, eluted with EtOAc, and evaporated *in vacuo*. The residue was then dissolved in 0.3 mL pyridine and trimethylacetyl chloride (50 □L, 0.406 mmol) was added. The mixture was then heated to 50 ºC for 30 min. The cooled reaction mixture was then applied to a column of silica (3 x 2 cm) and eluted with 20:1 Hex/EtOAc to afford pivalate ester **24** (24.7 mg, 87%) as a white solid. R_F = 0.33 (10:1 Hexane:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.29 (d, *J* = 6 Hz, 1H), 5.90 (dd, *J* = 2.5, 5 Hz, 1H), 5.77 (s, 1H), 5.33 (d, *J* = 2.5 Hz, 1H), 4.35 (ddd, *J* = 1, 5.5, 9 Hz, 1H), 4.29 (d, *J* = 15.5 Hz, 1H), 4.13 (ddd, *J* = 2, 2, 16 Hz, 1H), 2.24 (ddd, *J* = 2.5, 13.5, 13.5 Hz, 1H), 1.95 (ddd, *J* = 3, 14, 14 Hz, 1H), 1.85 (dddd, *J* = 3.5, 3.5, 6.5, 13 Hz, 1H), 1.70 (m, 1H), 1.6-1.55 (m, 2H), 1.43 (s, 3H), 1.39-1.23 (m, 2H), 1.35 (s, 3H), 1.19 (s, 9H), 1.08 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.2, 152.6, 138.5, 134.2, 134.1, 131.4, 118.8, 99.7, 86.8, 67.7, 60.4, 46.2, 39.0, 38.5, 36.7, 36.0, 27.2, 26.8, 26.1, 25.2, 24.9, 23.9, 23.8; IR (Neat Film NaCl) 3049, 2980,

2938, 1724, 1455, 1379, 1279, 1224, 1152, 1093, 1028, 976, 865 cm^{-1}; HRMS *m/z* calc'd for $C_{25}H_{36}O_4$ $[M]^+$: 400.2614, found 400.2610; $[\alpha]_D^{23.7}$ –533.13 (*c* 1.185, $CHCl_3$).

*4.19. Conversion to cyclopentanone **25***

Compound **23** (262 mg, 0.608 mmol) was dissolved in 5 mL THF and cooled with an ice bath. TBAF (1.0M in THF, 2.4 mL, 2.4 mmol) was added dropwise and the ice bath was removed. After stirring at ambient temperature for 2 hours, the volatiles were evaporated *in vacuo* to leave a viscous orange residue which was applied to a 3 x 2 cm plug of silica gel and eluted with 3:1 Hex/EtOAc (~350 mL total). Evaporation *in vacuo* provided a residue that was dissolved in 3 mL EtOAc and cooled with an ice bath. Pd/C was added (5 wt% Pd, 65.4 mg, 0.0307 mmol Pd, 5 mol%). The atmosphere was evacuated three times, filling with H_2 (balloon) each time. The reaction was stirred at 0 °C for 2.5 hours, with monitoring by TLC ($AgNO_3$ treated silica plates, 5:1 Hex/EtOAc). Once complete, the reaction was filtered through a 3 x 1 cm plug of silica gel and rinsed with ~65 mL EtOAc. Evaporation *in vacuo* afforded a residue that was dissolved in 3 mL CH_2Cl_2. To the solution was added 413.2 mg 4Å molecular sieves, NMO (110.8 mg, 0.946 mg, 1.5 equiv), and then TPAP (10.6 mg, 0.0302 mmol, 5 mol%). The reaction was allowed to stir 40 min and was then filtered through a 3 x 1 cm plug of silica gel which was rinsed with ~50 mL EtOAc. Evaporation *in vacuo*, followed by silica gel chromatography (2 x 12 cm, 10% Et_2O in petroleum ether) afforded cyclopentatnone **25** (174 mg, 90% over three steps) as a viscous colorless oil. R_F = 0.16 (10:1 Hexane:EtOAc), 0.36 (5:1 Hex:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (s, 1H), 4.40-4.30 (m, 1H), 4.27 (d, *J* = 15 Hz, 1H), 4.14 (ddd, *J* = 2, 2, 15 Hz, 1H), 2.71-2.58 (m, 2H), 2.52 (ddd, *J* = 4.5, 9.5, 18 Hz, 1H), 2.42 (ddd, *J* = 10, 10, 18 Hz, 1H), 2.24 (ddd, *J* = 2.5, 13.5, 13.5 Hz, 1H), 1.89-1.83 (m, 1H), 1.74-1.66 (m, 2H), 1.61 (ddd, *J* = 3.5, 5, 14 Hz, 1 H), 1.57-1.50 (m, 2H), 1.43 (s, 3H), 1.39-1.34 (obsc m, 1H), 1.36 (s, 3H), 1.07 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 222.2, 146.3, 133.8, 132.4, 120.5, 99.5, 67.4, 60.5, 51.5, 37.9, 36.7, 36.7, 36.1, 28.4, 26.9, 26.5, 25.3, 25.2, 23.5, 20.0; IR (Neat Film NaCl) 2982, 2937, 1743, 1445, 1378, 1224, 1090, 1026, 863 cm^{-1}; HRMS *m/z* calc'd for $C_{20}H_{28}O_3$ $[M]^+$: 316.2039, found 316.2030; $[\alpha]_D^{25.2}$ –91.95 (*c* 0.695, $CHCl_3$).

*4.20. Installation of isopropyl (preparation of compound **26**)*

A solution of ketone **25** (42.9 mg, 0.136 mmol, evaporated twice from benzene) dissolved in 0.5 mL THF and cooled to –78 °C was added via teflon cannula to a solution of KHMDS (37.2 mg, 0.186 mmol) in 0.6 mL THF at –78 °C with a 0.5 mL rinse. The mixture was stirred 30 min and then added, via Teflon cannula, to a solution of $PhNTf_2$ (70 mg, 0.196 mmol, evaporated twice from benzene) in 1 mL THF at –78 °C. After 50 min, silica gel was added and the suspension allowed to warm to ambient temperature. After evaporation *in vacuo*, the solid mixture was subjected to flash chromatography (2 x 12 cm, 5% Et_2O in petroleum ether) to afford a vinyl triflate (36 mg, 59% yield) as a colorless oil. R_F = 0.2 (20:1 Hexane:EtOAc); ^{1}H NMR (300 MHz, C_6D_6) δ 5.33 (bs, 1H), 5.22 (dd, *J* = 2.4, 2.4 Hz, 1H), 4.31-4.21 (m, 1H), 4.18-4.06 (m, 2H), 2.59 (ddd, *J* = 2.4, 2.4, 20.7 Hz, 1H), 2.49 (ddd, 2.4, 2.4, 20.7 Hz, 1H), 1.96 (ddd, *J* = 3.3. 13.8, 13.8 Hz, 1H), 1.80-1.68 (m, 2H), 1.62 (ddd, *J* = 3, 13.8, 13.8 Hz, 1H), 1.45-1.12 (m, XH), 1.40 (s, 3H), 1.36 (s, 3H), 1.05 (s, 3H), 0.96 (ddd, *J* = 3, 4.2, 14.4 Hz, 1H), 0.81 (s, 3H).

The vinyl triflate prepared above was evaporated twice from benzene. CuI (1.8 mg, 0.00945 mg, 12 mol%) and THF (0.65 mL) were added under an atmosphere of argon and the suspension cooled to –15 °C. *i*-PrMgCl (1.91 M in THF, 0.13 mL, 0.248 mmol, 3.1 equiv) was added quickly and the reaction turned from blue to green to yellow brown. The reaction mixture was kept between –20 and –15 °C for 2.5 hrs and then warmed with an ice bath and silica gel added. After evaporation *in vacuo*, the solid mixture was subjected to flash chromatography (3 x 2 cm, 5% Et_2O in petroleum ether) to afford compound **26** (23.5 mg, 85%, contaminated with ~10% reduction product) as a colorless oil. R_F = 0.43 (20:1 Hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.62 (bs, 1H), 5.37 (dd, *J* = 2.4, 2.4 Hz, 1H), 4.39-4.31 (m, 1H), 4.26 (d, *J* = 15 Hz, 1H), 4.16 (ddd, *J* = 1.5, 1.5, 15 Hz, 1H), 2.59 (ddd, *J* = 2.1, 2.1, 21.6 Hz, 1H), 2.49 (ddd, 2,1, 2.1, 21 Hz, 1H), 2.28 (ddd, *J* = 3.3, 13.2, 13.2 Hz, 1H), 2.14 (app pent, *J* = 6.9 Hz, 1H), 1.90-1.79 (m, 1H), 1.79-1.57 (m, 3H), 1.57-1.50 (m, 2H), 1.44 (s, 3H), 1.37 (s, 3H), 1.09 (s, 3H), 1.06 (d, *J* = 6.6 Hz, 3H), 1.04 (d, *J* = 6.6 Hz, 3H), 0.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 150.9, 134.9, 130.9, 117.9, 117.6, 99.4, 67.7, 60.5, 52.8, 38.3, 37.8, 37.3, 35.9, 30.6, 26.8, 25.5, 25.4, 25.3, 25.0, 24.9, 23.6, 21.4; IR (Neat Film NaCl) 3044, 2956, 2935, 1651, 1455, 1377, 1223, 1091, 863, 755 cm^{-1}; HRMS *m/z* calc'd for $C_{23}H_{33}O_2$ $[(M+H)-H_2]^+$: 341.2481, found 341.2489; $[\alpha]_D^{24.4}$ –169.01 (*c* 0.075, $CHCl_3$).

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Supplementary Material

Supplementary material includes selected spectra of new synthetic compounds.

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