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\[ \text{ring-closing metathesis} \quad \text{Knoevenagel cyclization} \]
\[ \text{Pd-catalyzed allylic alkylation} \quad \text{Noyori transfer hydrogenation} \]
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.

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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. Various members of the family have displayed interesting anticancer and antibacterial activity. In 2005, Sterner and co-workers reported the isolation of structurally similar diterpenoids, the heptemerones, from the mushroom Coprinus heptemerus. 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 one of the biggest synthetic challenges posed by these targets.

![Figure 1. Representative members of the guanacastepene and heptemerone diterpenoids.](image)

Although initial excitement over this family of natural products has tempered, due to their hemolytic activity, the synthetic community continues to demonstrate interest in these molecules. 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. At the same time, we had a burgeoning interest in deploying this technology in natural product synthesis, 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. The acetonide-protected diol would arise through reduction of the corresponding ketoester. We envisioned 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 styril moiety in cycloheptenone 3 would be installed by performing Stork–Danheiser chemistry on vinylogous ester 4. 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-cycloheptanone (6) 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 cyanofomate, 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 PPh3 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-lithioxystere to vinylogous ester 4 afforded cycloheptene 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. 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.

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. Houk’s work also revealed that steric effects, rather than torsional effects, were primarily responsible for the observed stereoselectivity.

Figure 2. Calculated (B3LYP/6-31+G(d), SMD) 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. 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.

With this result in hand, ketone (R)-4, of 83% ee, was prepared using (R)-t-BuPHOX and advanced to β-ketoester (R,R)-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. 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 diastereometric to 2, vide infra.

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 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 was not isolated. Instead it was immediately oxidized to aldehyde 13 with anhydrous MeNO₂. 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 to furnish β-ketoester 14. To our delight, heating 14 with NaOEt affected the Knoevenagel cyclization 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 allylic 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. The authors found that solvent choice was critical to the regioselectivity, as use of CH₂Cl₂ 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.

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.

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 Cs₂CO₃, 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 insufficient cooling of the exothermic lithium-halogen exchange reaction when performed in large volumes of THF. Changing the solvent to Et₂O alleviated this problem. However, attempts to heat the mixture of Et₂O 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°C. 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 cycloheptanone, we were able to synthesize 4.5 g of 18 as a pure, colorless oil.
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 Me₃NO. The aldehyde was then coupled to ethyl diazoacetate to furnish β-ketoester 20. Preliminary attempts at using an alkoxide base (NaOEt) to affect the desired Knoevenagel ring closure were successful, but we found that using KF as the base 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. By relying on reagent control of the newly formed stereocenter, we were able to address the low diastereoselectivity (~4:1) observed by Danishefsky, Snider, and Wicha. Ester 22 was then converted into acetone 23 using standard methods.

Scheme 8.

2.8. Attempts to functionalize the A ring

With acetone 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 acetone 23, we would generate the same intermediate ketone (I) used by Danishefsky and co-workers in their synthesis of guanacastepene A. This same intermediate would also be directly applicable to heptemerone G.

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. 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 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.

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 trisubstituted 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 sequence (Scheme 11, box) in order to install the C12 isopropyl and C14 ketone. Our prospects were bolstered by precedent from the Phillips and Mander 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 1H 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 CeCl₃. 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. 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 alklylation reactions to generate the two all carbon quaternary stereocenters with high fidelity. We have also identified conditions through which oxygenation and catalyzed decarboxylative allylic alklylation reactions to generate

4. Experimental section

Unless otherwise stated, reactions were performed in flame-dried glassware under an Ar or N₂ 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 °C, 20 mmHg) and stored under Ar in a Schlenk flask. Allyl cyanofomrate, TBSCI, and Ru[(S,S)-Ts-DPEN]₄ were prepared by known methods. (S)- and (R)-1-t-Butyloxycyclohexane was prepared by known methods. (R)-t-Leucinol was resolved using a known procedure. 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 light. Optical rotations were measured with a Jasco P-1010 polarimeter (10:1 hexanes:EtOAc). 1H and 13C NMR spectra were recorded on a Varian Unity Inova 500 (500 MHz and 125 MHz, respectively), and are reported relative to 2,2-dimethyl-2-silapentane-5-sulfonic acid (DSS).
In a nitrogen filled glove box, a flask was charged with Pd(dmbda) (568.4 mg, 0.697 mmol, 2 mol%), (R)-Bu-PHIX (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 glove box, 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 (8.0542 g, 95 % yield, >10:1 ratio of diastereomers). Rf value of minor diastereomer: 0.40 (10:1 Hexane:EtOAc); \( \delta \) 7.8335 g, 33.14 mmol) in 15 mL THF and cooled to 0 °C. NaH (60% dispersion in mineral oil, 34.8 mg, 0.87 mmol) was added and the mixture allowed to warm to ambient temperature. The aqueous layer was washed 3 x 10 mL H2O and 10 mL EtO. The combined organic layers were dried with MgSO4 and evaporated in vacuo. The crude residue was then dissolved in 3 x 10 mL EtO and the combined organic layers dried with MgSO4 and evaporated in vacuo. Flash chromatography (2 x 14 cm, 10.1 Hex/EtOAc) afforded \( \beta \)-ketoester \( \text{9} \) (213.3 mg, 74% yield, 1:diastereomer) as a yellow oil. Rf = 0.36 (5:1 Hexane:EtoAc); \( \delta \) 7.638 (\( d = 2.7, 2.7, 5.4, 1H, 1H \)), 6.15-6.10 (10 mL, (1H), 5.95 (\( d = 5.4, 5.4, 10.8, 16.8 Hz, 1H \)), 5.67 (s, 1H); 5.34 (\( d = 1.5, 1.5, 15.4, 17 Hz, 1H \)), 5.22 (\( d \equiv 1.5, 1.5, 10.5, 17 Hz, 1H \)), 4.74-4.62 (2H), 2.81 (\( d = 2.7, 14.7, 14.7 Hz, 1H \)), 2.55 (bd, (1H)), 2.41 (\( d = 1.5, 3, 18 Hz, 1H \)), 2.11 (\( d = 2.2, 1.4, 17 Hz, 1H \)), 1.81 (\( d = 2.7, 6, 14.7 Hz, 1H \)), 1.70 (\( d = 1.8, 5.7, 14.4 Hz, 1H \)), 1.48 (s, 3H), 1.25 (s, 3H).

A flame-dried vial was charged with Pd(dmbda) (4.5 mg, 0.000552 mmol, 5 mol%), (S)-Bu-PHIX (2.5 mg, 0.00645 mmol, 5.8 mol%), and 3 mL THF. The mixture was stirred at 25 °C for 30 min at which time \( \beta \)-ketoester \( \text{9} \) (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 ratio of diastereomers). Rf = 0.40 (10:1 Hexane:EtoAc); \( \delta \) 7.638 (\( d = 3, 3, 5, 1H, 1H \)), 6.09 (\( d = 1.8, 1.8, 5.4, 5H, 1H \)), 5.71 (s, 1H), 5.61 (\( d = 6.9, 7.5, 10.2, 18 Hz, 1H \)), 5.06-4.97 (2H), 2.55-2.41 (2H), 2.35 (\( d = 1.8, 2.7, 18 Hz, 1H \)), 2.26-1.93 (2H), 1.70 (app d, \( d = 5.1, 1H, 1H \)), 1.64 (app d, \( d = 5.7 Hz, 1H \)), 1.12 (s, 3H), 1.07 (s, 3H); \( \delta \) 7.54 (s), 1.15 (s), 1.11 (s), 1.13 (s); \( \delta \) 7.54 (\( d = 3, 3, 5, 1H, 1H \)), 6.09 (\( d = 1.8, 1.8, 5.4, 5H, 1H \)), 5.71 (s, 1H), 5.61 (\( d = 6.9, 7.5, 10.2, 18 Hz, 1H \)), 5.06-4.97 (2H), 2.55-2.41 (2H), 2.35 (\( d = 1.8, 2.7, 18 Hz, 1H \)), 2.26-1.93 (2H), 1.70 (app d, \( d = 5.1, 1H, 1H \)), 1.64 (app d, \( d = 5.7 Hz, 1H \)), 1.12 (s, 3H), 1.07 (s, 3H); \( \delta \) 7.54 (s); 1.15 (s), 1.11 (s);-C NMR (75 MHz, CDCl3) \( \delta \) 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, 2829, 1656, 1625, 1450, 1375, 1202, 1122, 913 cm-1.

To a solution of hexamethylsilazane (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
A 3000 mL flask was charged with (4R,7R)-4,7-diallyl-4,7-dimethyl-3-styrylcyclohept-2-enone (11, 8.1630 g, 25.47 mmol) and 2000 mL CHCl₃. 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% Et₂O in hexane) afforded the title compound as a yellow oil (5.3386 g, 89% yield with 6% starting material). Rf = 0.40 (10:1 Hexane:EtOAc); ²H NMR (500 MHz, CDCl₃) Major diastereomer: δ 7.44-7.41 (m, 2H), 7.37-7.33 (m, 2H), 7.30-7.26 (m, 1H), 7.69 (d, J = 16.5 Hz, 1H), 6.82 (d, J = 15.5 Hz, 1H), 3.61 (s, 1H), 2.95 (d, J = 5.5, 5.5, 11.5 Hz, 2.25 Hz, 1H), 5.61 (ddd, J = 7, 8.5, 10.5, 17 Hz, 1H), 5.31 (J = 1.5, 1.5, 17 Hz, 1H), 5.26-5.21 (m, 1H), 5.06-4.99 (m, 2H), 4.70-4.56 (m, 2H), 2.41-2.42 (m, obsd cm, 1H), 2.16 (app dd, J = 8, 14, 14 Hz, 1H), 1.79 (obsb ddh, 2H), 1.66 (ddd, J = 1, 9, 10 Hz, 2H), 1.47 (s, 3H), 1.26 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) 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, 131.7, 131.7, 128.7, 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) 3076, 3025, 2974, 2934, 1734, 1653, 1648, 1584, 1448, 1375, 1211, 1196, 103, 918, 918 cm⁻¹; HRMS m/z calc’d for C₂₉H₂₆O + [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(dmdba)₂ (440.2 mg, 0.540 mmol, 2 mol%), and (R)-Bu-PHOX (253.0 mg, 0.653 mmol, 2.4 mol%) and 2500 mL THF. The mixture is stirred at 30 min, at which time (5R)-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). Rf = 0.52 (10:1 Hexane:EtOAc); ¹H NMR (300 MHz, CDCl₃) 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, 1H), 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) δ 209.4, 154.8, 136.7, 133.7, 133.7, 132.8, 128.7, 128.0, 126.8, 125.2 (118.1, 118.0, 52.8, 46.7, 45.3, 44.4, 34.3, 29.8, 25.6, 22; IR (Neat Film NaCl) 3076, 3027, 2976, 2931, 1659, 1587, 1449, 1373, 1194, 1147, 1120, 962, 915, 753, 694 cm⁻¹; FAB⁺ HRMS m/z calc’d for C₂₉H₂₆O [M+H]+: 321.2218, found 321.2225; [α]D20⁴⁰ +87.18 (c 1.27, CHCl₃), 10.1 dr, Anti-Me diastereomer 97% ee).
A vial was charged with a mixture of (1R,6R,8aS)-6-allyl-1-(tert-butyldimethylsilyloxy)-6a-dimethyl-6,7,8a-tetrahydroazulen-5(1H)-one (18). A solution of (1R,6R,8aS,Z)-6-allyl-1-hydroxy-6,8a-dimethyl-6,7,8,8a-tetrahydroazulen-5(1H)-one (17, 3.978 g, 17.3 mmol) in 84 mL CH₂Cl₂ was cooled to –78 °C. To this mixture was added 2,6-lutidine (86 mL, 68.68 mmol, 4 equiv.), followed by TBSOTf (5.25 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. NaHCO₃. The mixture was allowed to thaw and the layers separated. The aqueous layer was washed with EtOAc (3 x 100 mL) and the combined layers dried with MgSO₄. 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 (4,548 g, 77% yield). Rₚ = 0.17 (20:1 Hexane/EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 6.23 (d, J = 5.5 Hz, 1H), 6.19 (d, J = 2.5, 5 Hz, 1H), 5.84 (dd, J = 7, 8, 12.5, 15 Hz, 1H), 5.78 (s, 1H), 5.06-5.01 (m, 2H), 2.43 (d, J = 2.5, 14.5 Hz, 1H), 2.48 (d, J = 7, 13.5 Hz, 1H), 2.31 (dd, J = 2.5, 14.5, 15 Hz, 1H), 2.20 (d, J = 8, 14 Hz, 1H), 2.04 (d, J = 2.5, 14.5 Hz, 1H), 1.59 (dd, J = 2.5, 5.5, 14.5 Hz, 1H), 1.46 (dd, J = 2, 5.5, 14.5 Hz, 1H), 1.15 (s, 3H), 1.06 (s, 3H), 0.90 (s, 3H), 0.98 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 208.3, 162.4, 141.6, 136.2, 122.0, 117.4, 51.7, 48.4, 43.8, 31.0, 27.9, 27.6, 25.8, 24.4, 18.3, 4.3, 4.7; IR (Neat Film NaCl) 3063, 2956, 2928, 1725, 1654, 1636, 1472, 1451, 1382, 1361, 1250, 1095, 936, 870, 837, 775 cm⁻¹; HRMS m/z calc’d for C₇₆H₁₁₂O₃Si [M⁺] + 1342.7238, found 1342.7236 (c 1.56, CHCl₃).

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

A 250 mL round-bottom flask was charged with 3-[(1R,6R,8aS,Z)-1-(tert-butyldimethylsilyloxy)-6a-dimethyl-5-oxo-1,5,6,7,8a-hexahydroazulen-6-yl]propanol (19, 3.7336 g, 10.30 mmol) and 100 mL CH₂Cl₂. Anhydrous SnCl₄ (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 mL, 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 (0.4558 g, 88% yield). Rₚ = 0.28 (5:1 Hexane/EtOAc); Major keto tautomer: ¹H NMR (500 MHz, CDCl₃) 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), 2.53 (m, 1H), 2.47 (m, 1H), 2.36 (dd, J = 2.5, 14.5, 14.5 Hz, 1H), 2.10 (dd, J = 2.5, 14.5, 14.5 Hz, 1H), 2.02 (ddd, J = 6.5, 9.5, 14.5 Hz, 1H), 1.72 (m, J = 6, 9.5, 14 Hz, 1H), 1.54 (ddd, J = 2.5, 14.5, 14 Hz, 1H), 1.17 (s, 3H), 1.06 (s, 3H), 0.89 (s, 3H), 0.90 (s, 3H), 0.83 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 207.9, 207.2, 162.6, 141.9, 136.1, 121.8, 85.0, 49.3, 39.8, 31.6, 31.2, 27.8, 27.4, 25.8, 18.2, 14.3, –4.7; IR (Neat Film NaCl) 2958, 2926, 2928, 1725, 1654, 1636, 1472, 1451, 1382, 1361, 1250, 1095, 936, 870, 837, 775 cm⁻¹; HRMS m/z calc’d for C₇₆H₁₁₂O₃Si [M⁺] + 1342.7227, found 1342.7226 (0.45, CHCl₃).
4.15. Knoevenagel cyclization (preparation of compound 21)

To a solution of ethyl 5-((1R,6R,8aS,Z)-1-(tert-butylidimethylsilyl)-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 ºC 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. Rₚ = 0.29 (5:1
Hexane:EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 6.19 (d, J = 5.5
Hz, 1H), 6.13 (dd, J = 2, 5.5 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 (dd, J = 5.5, 5.5, 11.5 Hz,
1H), 1.62 (dd, J = 2, 7, 15 Hz, 1H), 1.37 (ddd, J = 2, 7, 15.5, 15.5
Hz, 1H), 1.27 (dd, J = 7, 7.5 Hz, 3H), 1.22 (s, 3H), 1.05 (s, 3H), 0.89
(s, 9H), 0.82 (s, 3H), 0.70 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) 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, 24.6, 18.2, 14.1, 4.3, 4.7; IR (Neat Film NaCl) 3049, 2980,
1650, 1572, 1463, 1450, 1362, 1256, 1059, 1005, 870, 836, 774 cm⁻¹;
FAB⁺ HRMS m/z calc'd for C₆H₆O₂Si [M+H]⁺: 413.2618, found 413.2614;
[δ]D²⁴ = +790.69 (c 1.945, CHCl₃).

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%). Rₚ = 0.26 (5:1
Hexane:EtOAc); ¹H NMR (500 MHz, CDCl₃, 50 ºC) δ 6.21 (s,
J = 6.15 Hz, 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, 11.5 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
dd, 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, 7.5 Hz, 3H), 1.05 (s, 3H), 1.00 (s, 3H),
0.90 (s, 9H), 0.82 (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 C₆H₆O₂Si [M+H]⁺:
432.2696, found 432.2716; [δ]D²⁴ = +707.61 (c 0.620, CHCl₃).
Note: due to conformational instability, we were unable to obtain a
suitable ¹³C NMR spectrum.

4.17. Conversion to acetone 23

Compound 23 (30.5 mg, 0.708 mmol) was dissolved in 0.2 mL
THF and TBAF (1.0 M in THF, 150 µL, 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 µL, 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 paving ester 24 (24.7 mg, 87%) as a
white solid. Rₚ = 0.33 (10:1 Hexane:EtoAc); ¹H NMR (500 MHz,
CDCl₃) δ 6.29 (d, J = 6 Hz, 1H), 5.90 (dd, J = 2.5, 5.5 Hz,
1H), 5.77 (s, 1H), 5.33 (d, J = 2.5 Hz, 1H), 4.35 (ddd, J = 1, 5.5,
9.9 Hz, 1H), 4.29 (d, J = 15.5 Hz, 1H), 4.13 (ddd, J = 2, 2, 16
Hz, 1H), 2.24 (dd, J = 2, 2.5, 15.5 Hz, 1H), 1.95 (ddd, J = 3,
14, 14 Hz, 1H), 1.85 (ddd, 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); ¹³C NMR (125 MHz,
CDCl₃) δ 178.2, 152.6, 138.5, 134.2, 131.4, 113.1, 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,
followed by silica gel chromatography (2 × 12 cm, 10% Et2O in petroleum ether) to afford a vinyl triflate (36 mg, 59% yield) as a colorless oil. Rf = 0.2 (20:1 Hexane:EtOAc); 1H NMR (300 MHz, CD2Cl2) δ 5.53 (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 (dd, J = 2.4, 2.4, 20.7 Hz, 1H), 2.49 (ddd, J = 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 (dd, J = 3, 13.8, 13.8 Hz, 1H), 1.45-1.12 (m, CHX), 1.40 (s, 3H), 1.36 (s, 3H), 1.05 (s, 3H), 0.96 (dd, J = 3, 4.2, 14.4 Hz, 1H), 0.81 (s, 3H).

The vinyl triflate prepared above was evaporated twice from benzene. Cul (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-Pr2MgCl (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 × 2 cm, 5% EtOAc in petroleum ether) to afford compound 25 (23.5 mg, 85%, contaminated with −10% reduction product) as a colorless oil. Rf = 0.43 (20:1 Hexane:EtOAc); 1H NMR (300 MHz, CDCl3) 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, 15, 15 Hz, 1H), 2.59 (dd, J = 2.1, 2.1, 21.6 Hz, 1H), 2.49 (ddd, J = 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, 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, 1H), 1.04 (d, J = 6.6 Hz, 0.99 Hz, 3H), 1.03 (s, 3H); 13C NMR (125 MHz, CDCl3) 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, 25.2, 25.0, 24.9, 23.6, 21.4; IR (Neat Film NaCl) 3044, 2956, 2935, 1651, 1455, 1377, 1223, 1091, 883, 755 cm−1; HRMS m/z calc’d for C23H45O2 [(M+H)-H2O]+: 341.2489, found 341.2489; [α]D544−169.01 (c 0.075, CHCl3).

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Supplementary Material

Supplementary material includes selected spectra of new synthetic compounds.

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