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Enantioselective syntheses of tremulenediol A and tremulenolide A

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Abstract—A concise entry to the skeleton of the tremulane sesquiterpenes is described that culminated in the first enantioselective syntheses of tremulenediol A and tremulenolide A. The approach features a series of efficient transition metal-catalyzed reactions commencing with an enantioselective rhodium(II)-catalyzed intramolecular cyclopropanation followed by a regioselective allylic alkylation and a diastereoselective rhodium(I)-catalyzed [5+2] cycloaddition.

1. Introduction

The tremulanes constitute a novel class of sesquiterpene natural metabolites that is characterized by an unusual carboskeletal array **1** isomeric to the lactarane skeleton (**2**).[1] Tremulenolide A (**3**) and tremulenediol A (**4**) are two representative tremulanes that were isolated in 1993 from the fungal pathogen *Phellinus tremulae* during the course of a project to develop tactics to control fungal decay and staining in trembling or quaking aspen (*Populus tremuloides*).[1] Aspen represents 11% of the entire Canadian timber resource and 54% of the net merchantable hardwood timber. *P. tremulae*, the most serious wood rotting pathogen of aspen in Canada, greatly reduces the potential economic value of this timber reserve (Fig. 1).

Although the commercial advantages associated with the potential biological activity of these two natural products are of considerable interest in itself, the structural features of the skeletal core of **3** and **4** present an even greater stimulus to their selection as synthetic targets. For example, in 1998 Davies and Doan reported the syntheses of racemic **3** and **4** in overall yields of 0.8 and 0.9%, respectively.[2] His strategy featured the cyclopropanation of an appropriately functionalized diene with the requisite vinylcarbenoid followed by a Cope rearrangement of the intermediate divinylcyclopropane generated in situ to assemble the seven-membered ring of the hydroazulene core with a high level of relative stereoselectivity.[3,4] However, efforts to apply this plan to an efficient enantioselective synthesis using a chiral dirhodium(II) catalyst were unsuccessful.

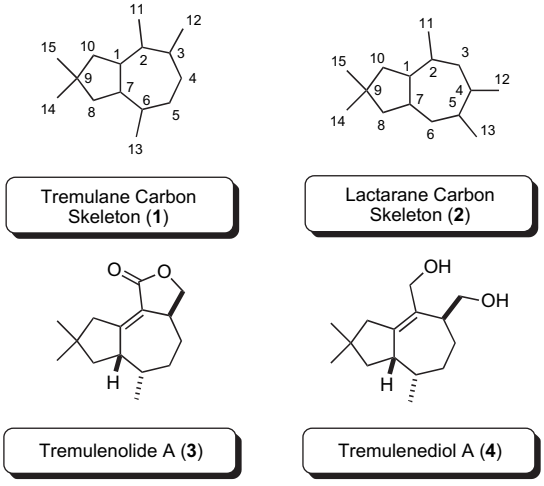

Figure 1.

We have long been interested in developing methods for the enantioselective synthesis of biologically relevant natural products. In this context, the 2,3,6,9-substitution pattern on the bicyclo[5.3.0]decane skeleton and the relative configurations of the three stereogenic centers on the seven-membered ring captured our attention as being well suited for application of synthetic methodology that was being contemporaneously developed by our group.

The initial stimulus for our general approach to the tremulane skeleton **5**, which is outlined in Scheme 1, was a report by Wender that vinylcyclopropanes with tethered alkyne functional groups could undergo diastereoselective intramolecular rhodium(I)-catalyzed [5+2] cycloadditions to give hydroazulenes.[5] Based upon this account, we reasoned that an intermediate such as **6** might be accessible by allylic

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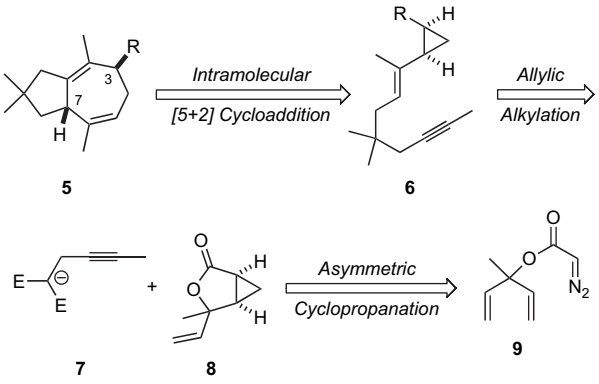
alkylation of the vinylcyclopropyl lactone **8** that would in turn arise from an intramolecular cyclopropanation of the divinyl diazoacetate **9**. We had previously demonstrated that vinylcyclopropanes related to **8** underwent several kinds of regioselective allylic alkylations via a S_N2'-like manifold.[6] Because the stereochemistry at C(3) and C(7) of **5** is established in the cyclopropanation step, it occurred to us that **8** should be accessible via an enantioselective cyclopropanation using the chiral carboxamide dirhodium(II)-catalysts we had developed in collaboration with Doyle.[7] Our recent total synthesis of ambruticin establishes a benchmark for the application of this method to the construction of complex natural products.[8,9] This methodology has also been used for the synthesis of conformationally constrained peptide analogs to study protein–ligand interactions.[10]



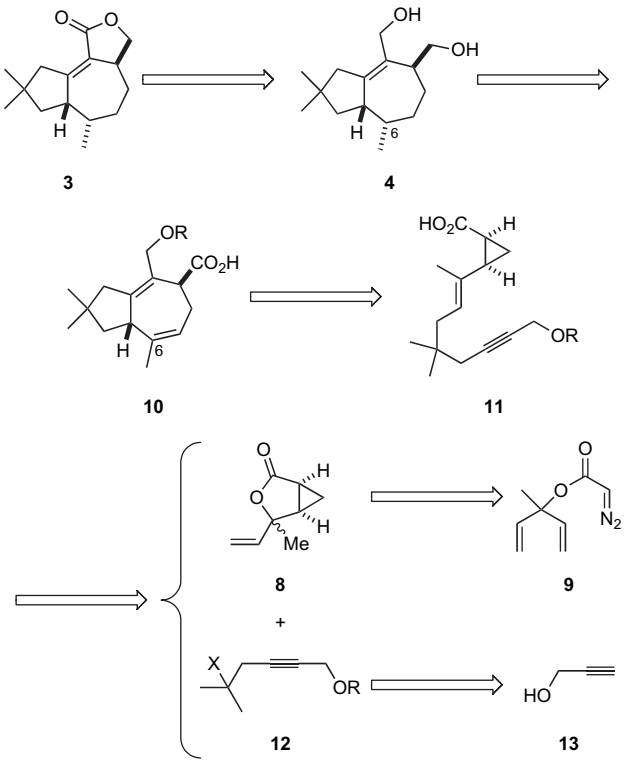
Scheme 1.

Having thus formulated our overall strategy, we set to the task of synthesizing tremulenolide A (**3**) and tremulenediol A (**4**). These efforts recently culminated in the first enantioselective entry to this class of sesquiterpene natural products.[11] We were also intrigued by the possibility of conducting one or more of the transition metal-catalyzed transformations in one pot to streamline the overall operation, and this hypothesis led to the development of some novel tandem reactions.[12] We now report some details of these investigations.

2. Results and discussion

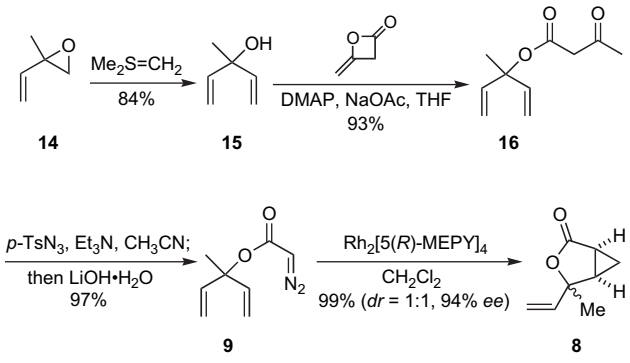
2.1. First generation strategy

Our first generation approach toward the tremulane sesquiterpenes is illustrated in Scheme 2. We envisioned that tremulenolide A (**3**) would arise from an allylic oxidation of the diol moiety in tremulenolide A (**4**), which would be readily accessible via refunctionalization of **10**. The selective hydrogenation of the trisubstituted $\Delta^{5,6}$-double bond in **10** was anticipated to proceed preferentially from the less hindered face. The hydroazulene **10** would then in turn be derived from enyne **11** via a diastereoselective rhodium(I)-catalyzed intramolecular [5+2] cycloaddition. An organocopper mediated S_N2' ring opening of lactone **8** with alkyl halide **12** would lead to the vinylcyclopropane **11**, which comprises all the carbon atoms present in **3** and **4**. As noted previously, **8** would be prepared from the enantioselective, intramolecular rhodium(II)-catalyzed cyclopropanation of diazoester **9**, whereas propargyl alcohol (**13**) was viewed as a suitable precursor of **12**.



Scheme 2.

The opening move in the synthesis was the enantioselective construction of cyclopropyl lactone **8** via a straightforward four-step sequence of reactions beginning with commercially available 2-methyl-2-vinyl oxirane (**14**) (Scheme 3). Thus, treatment of oxirane **14** with the sulfur ylide of trimethylsulfonium iodide followed by spontaneous β-elimination of dimethylsulfide provided the known divinyl carbinol **15** in 84% yield.[13] Subsequent acylation of **15** with diketene in the presence of 4-dimethylaminopyridine (DMAP) and sodium acetate provided acetoacetate **16** in 93% yield. A one-pot diazo transfer reaction of **16** with *p*-toluenesulfonyl azide (*p*-TsN_3) and Et_3N, followed by hydrolytic cleavage of the ketone functionality with $LiOH\cdot H_2O$ provided diazoester **9** in 97% overall yield. The use of the Corey–Myers diazoesterification protocol to prepare **9** directly from **15** was also explored,[14] but the sterically hindered tertiary alcohol proved resistant to acylation under these conditions.

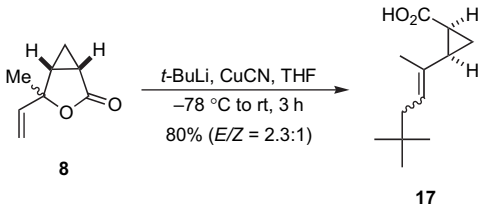


Scheme 3.

When diazoester **9** was exposed to 0.1 mol % of Rh_2[5(*R*)-MEPY]$_4$, intramolecular cyclopropanation proceeded

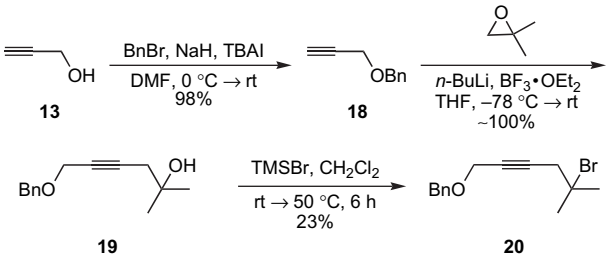
smoothly to yield the desired cyclopropyl lactone **8** as a mixture (1:1) of products epimeric at C(4) in 99% yield and 94% ee for each diastereomer.[7] The enantioselectivity of the cyclopropanation reaction was determined by treating the diastereomeric mixture of cyclopropyl lactones **8** with 1 equiv of phenyllithium to yield the corresponding diastereomeric ketones. Subsequent analytical chiral HPLC analysis of each ketoalcohol showed that the cyclopropanation of diazoester **9** proceeded in 94% ee and that a diastereomeric mixture of cyclopropyl lactones obtained in the cyclization is inconsequential because the epimeric center was slated for destruction in the next step of the synthesis. The optimized sequence provided the requisite cyclopropyl lactone **8** in 71% overall yield from **14**.

In order to examine the underlying feasibility of the proposed organocuprate-mediated S_N2' ring opening reaction, cyclopropyl lactone **8** was treated with the tertiary organocuprate reagent derived from *t*-BuLi and CuCN (Scheme 4).[15] Gratifyingly, the desired vinylcyclopropane **17** was obtained in 80% yield as a mixture (2.3:1) of *E*/*Z*-olefinic isomers. Thus, our strategy for preparing a vinylcyclopropane related to **11** appeared soundly based.



Scheme 4.

Buoyed with confidence that the more complex organocuprate reagent derived from alkyne **12** would behave similarly, we turned our attention toward the task of synthesizing the homopropargylic tertiary bromide **20** (Scheme 5). Toward this end, the alcohol **19** was first prepared in high overall yield by a simple two-step sequence of reactions. Propargyl alcohol (**13**) was first treated with BnBr and NaH in the presence of TBAI to yield **18** in 98% yield. The benzyl protecting group was selected in anticipation that it could be removed concomitantly with the catalytic hydrogenation that would reduce the $\Delta^{5,6}$-olefin later in the synthesis (vide supra). The homopropargyl alcohol **18** was converted into the alcohol **19** in nearly quantitative yield by sequential deprotonation with *n*-BuLi and reaction of the resultant acetylide anion with isobutylene oxide in the presence of $BF_3 \cdot OEt_2$. Unfortunately, conversion of alcohol **19** into the corresponding bromide **20** proved troublesome. After considerable experimentation, the conversion was effected using TMSBr in CH_2Cl_2,[16] but the reaction was inefficient, proceeding in a mere 23% yield.



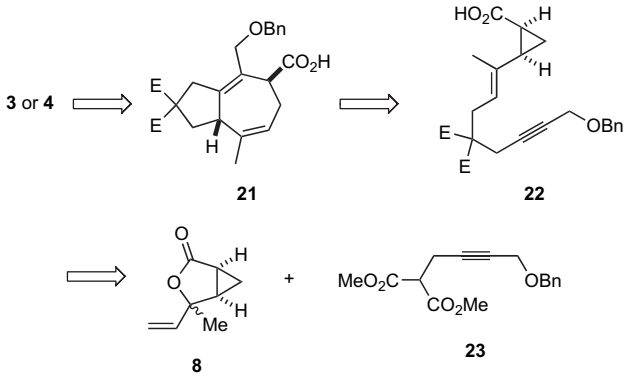
Scheme 5.

A number of conditions were screened, including, but not limited to, PBr_3, PBr_3 and pyridine, and TMSCl and LiBr; none of these procedures gave any better results. The instability of **20** no doubt contributed to the problem.

With limited quantities of bromide **20** in hand, we turned our attention toward coupling the derived organocuprate with cyclopropyl lactone **8**. However, perhaps not surprisingly, metallation of the tertiary homopropargylic halide **20** proved exceedingly difficult. Several attempts to effect metal–halogen exchange to give the derived organolithium or Grignard reagent were universally unsuccessful. It thus became apparent that introducing the *gem*-dimethyl moiety directly at an early stage would not be feasible, and a change in tactics was indicated.

2.2. Second generation approach: some initial studies

The difficulties that had been encountered in generating an unstabilized tertiary carbanion led us to consider a more traditional means of effecting the allylic alkylation of the cyclopropyl lactone **8** to provide a vinyl cyclopropane that would participate in the proposed [5+2] cycloaddition. We thus formulated the modified plan as summarized in Scheme 6 in which a conventional transition metal-catalyzed allylic alkylation of **8** served as a pivotal step. Indeed, we had previously shown that such lactones underwent highly regioselective, Pd(0)-catalyzed alkylations with stabilized carbanions to give the expected products in high yields.[6] The slight drawback of this approach relative to the original plan was the necessity of reducing the malonate moiety in an intermediate derived from **21** into a *gem*-dimethyl group. Nevertheless, the strategy was still concise and merited examination.

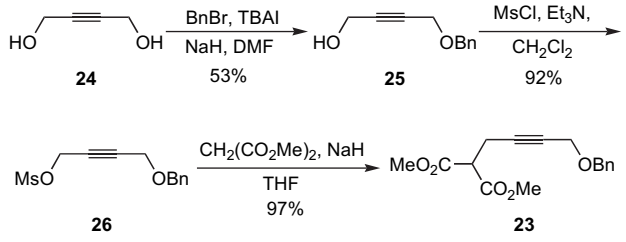


Scheme 6.

Because the cyclopropanation and the [5+2] cycloaddition steps in our synthetic plan were both rhodium catalyzed, we were intrigued by the notion that the allylic alkylation step might also be rhodium catalyzed. Hence, Evans' use of a modified Wilkinson's catalyst to promote allylic alkylations captured our attention.[17,18] We were of course cognizant of the fact that such reactions typically proceeded to give products in which the nucleophile attacked the *more* substituted terminus of the allylic moiety, irrespective of the structure of the starting material. Such a regiochemical outcome was *opposite* to that which was required for the problem at hand. Nevertheless, if $RhCl(PPh_3)_3/P(OMe)_3$ or another rhodium catalyst were capable of catalyzing the allylic alkylation of cyclopropyl lactone **8** to give **22**, the possibility of inducing

the subsequent intramolecular [5+2] cycloaddition in situ was too attractive to ignore. Such a tandem rhodium(I)-catalyzed allylic alkylation and [5+2] cycloaddition sequence would represent a novel and rapid entry to hydroazulenes in general and the tremulane bicyclic core in particular.

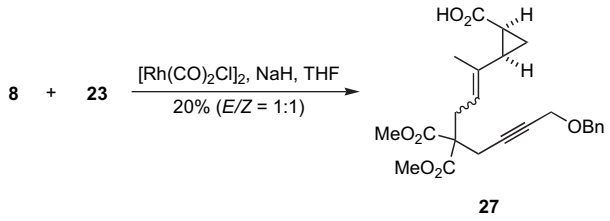
The malonate **23** was prepared in good overall yield from commercially available 2-butyn-1,4-diol (**24**) by a relatively straightforward sequence of reactions, although the monoprotection of **24** was somewhat problematic (Scheme 7). Initial experiments to monobenzylate **24** relied upon a report that showed symmetrical diols could be selectively monobenzylated with Ag_2O and benzyl bromide.[19] When diol **24** was treated with Ag_2O and BnBr, **25** was obtained, albeit in 51% yield. Given the modest yield and high cost of a silver-mediated monoalkylation procedure, more conventional benzylation methods were explored. In a preliminary experiment, the diol **24** was treated with BnBr and NaH, but **25** was obtained in only 17% yield. Changing the solvent from THF to DMF led to a slight increase in the yield to 24%. Finally, it was found that reaction of diol **24** with benzyl bromide, NaH, and tetrabutylammonium iodide (TBAI) in DMF, provided **25** in 53% yield. Subsequent treatment of propargyl alcohol **25** with methanesulfonyl chloride (MsCl) and Et_3N in CH_2Cl_2 provided the known mesylate **26** in 92% yield.[20] Treatment of mesylate **26** with sodiodimethyl malonate gave **23** in 97% yield. This three-step sequence enabled the production of multigram quantities of **23** in an overall yield of 48%.



Scheme 7.

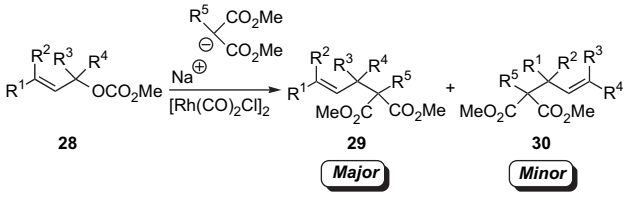
The stage was thus set to explore the transition metal-catalyzed allylic alkylation of **8** with the anion derived from **23**. Because of our penchant to develop novel rhodium-catalyzed domino reactions, we ignored the ample literature precedent that strongly suggested such a reaction involving **8** would proceed with the *incorrect* regiochemistry. In initial experiments we found that treating the cyclopropyl lactone **8** with the sodium enolate of malonate **23** in the presence of $RhCl(PPh_3)_3/P(OMe)_3$ gave no isolable alkylation product, even after extended reaction times and elevated temperatures. Because the dimeric rhodium(I) catalyst $[Rh(CO)_2Cl]_2$ was known to catalyze the intramolecular [5+2] cycloadditions,[21] we queried if perchance it might also catalyze allylic alkylations. In the event, reaction of **8** with the sodium salt of **23** in the presence of $[Rh(CO)_2Cl]_2$ afforded an *E*/*Z*-mixture (1:1) of **27** as the only isolable product, albeit in only about 20% (unoptimized) yield (Scheme 8).

Not only did we thus discover that $[Rh(CO)_2Cl]_2$ could catalyze allylic alkylations, but we also found that the regiochemistry of such reactions was opposite to that expected. This unexpected yet felicitous result led us to develop $[Rh(CO)_2Cl]_2$ as a novel catalyst for promoting allylic



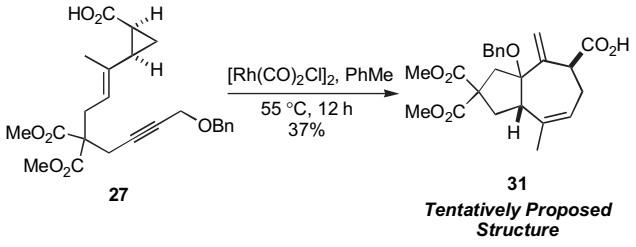
Scheme 8.

alkylations.[22] In exploring the scope of these processes, we showed that the reactions proceeded with good to excellent regioselectivity for a variety of allylic carbonates. The preferred product was generally the one in which the nucleophile became attached to the carbon bearing the carbonate leaving group, irrespective of the structure of the starting carbonate (Scheme 9). *The structure of the starting material generally maps directly on the product, an unusual phenomenon in transition metal-catalyzed allylic alkylations. Ignoring the considerable body of literature on the regiochemistry of Rh-catalyzed allylic alkylations thus paid considerable dividends.*



Scheme 9.

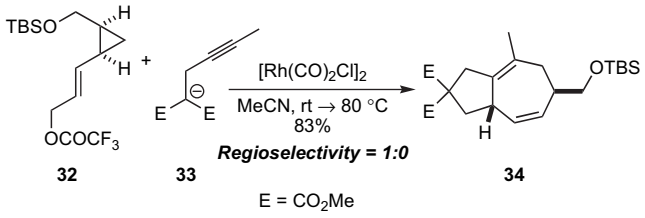
Encouraged by the formation of cyclopropyl enyne **27** from the $[Rh(CO)_2Cl]_2$-catalyzed reaction of **8** and the sodium salt of **23**, the feasibility of conducting a domino allylic alkylation/[5+2] cycloaddition sequence was examined. However, these exploratory experiments were unsuccessful, and none of the desired cycloadduct was obtained. It should be noted that there are no examples in the literature of rhodium-catalyzed [5+2] cycloadditions of *cis*-cyclopropyl enyne carboxylates like **27**.[5] In order to assess whether such compounds were suitable substrates for these carbocyclizations, a number of experiments were conducted in which the catalyst, additive, solvent, and temperature were varied to see whether **27** would cyclize as expected. In one of the experiment, a solution of **27** containing $[Rh(CO)_2Cl]_2$ in toluene was heated to 55 °C for 12 h to give a compound that has not been unequivocally identified, but the NMR spectral data are consistent with the tentatively assigned structure **31** (Scheme 10).



Scheme 10.

Although we were unsuccessful in developing a domino $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation and [5+2] cycloaddition route to **3** and **4**, we were able to apply such reactions

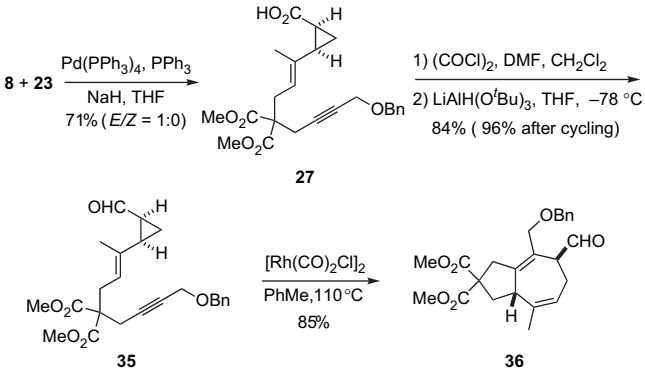
to simpler, yet closely related, substrates.[12] For example, reaction of **32** with the malonate anion **33** in the presence of $[Rh(CO)_2Cl]_2$ (5 mol %) led to the cycloadduct **34** in excellent overall yield (Scheme 11). The regio- and diastereoselectivity in this domino process was the same as that observed by Wender.[21]



Scheme 11.

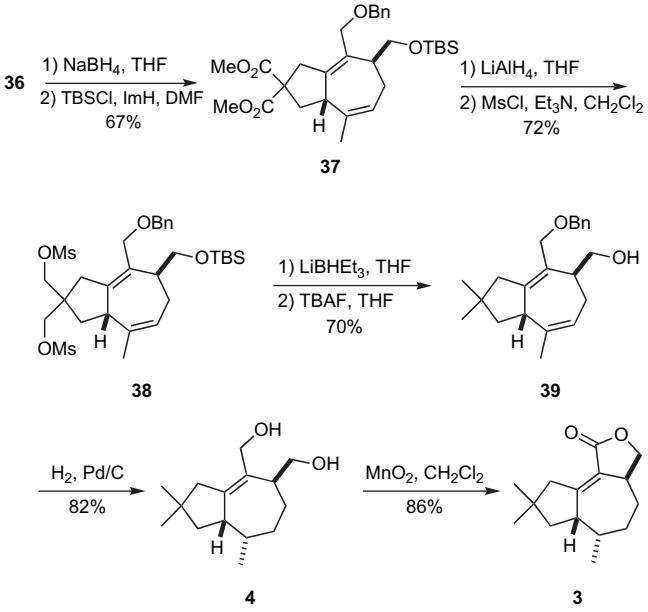
2.3. Second generation approach: successful endgame

Given the poor efficiency with which $[Rh(CO)_2Cl]_2$ catalyzed the allylic alkylation of cyclopropyl lactone **8** with malonate **23**, we decided to examine the use of the more traditional Pd(0) catalysts. After brief experimentation to optimize conditions, we found that the reaction of **8** with the sodium enolate of **22** in the presence of 10 mol % $Pd(PPh_3)_4$ and additional PPh_3 (70 mol %) provided enyne **27** in 71% yield (Scheme 12). The next stage of the sequence involved a [5+2] cycloaddition in which cleavage of the more substituted cyclopropane bond was needed to construct the requisite bicyclo[5.3.0]decane. Based upon results reported by Wender,[21] we reasoned that such cleavage would require that the carboxylic acid moiety in **27** be first reduced to the corresponding aldehyde. Thus, treatment of **27** with oxalyl chloride and DMF followed by reduction of the crude acid chloride with $LiAlH(O^tBu)_3$ provided aldehyde **35** in 84% yield.[23] The primary alcohol resulting from over-reduction was also obtained in 12% yield, but subsequent oxidation with Dess–Martin periodinane proceeded quantitatively to provide **35** in 96% overall yield. Heating **35** in the presence of $[Rh(CO)_2Cl]_2$ proceeded with high regioselectivity to furnish the desired cycloadduct **36** in 85% yield. The structure of **36** was assigned based upon analysis of the HMQC and HMBC NMR data, together with comparisons to Wender's reported spectral data for similar compounds.[21]



Scheme 12.

With cycloadduct **36** in hand, completion of the syntheses of **3** and **4** required a series of refunctionalizations. Thus, reduction of the aldehyde group in **36** with $NaBH_4$ followed by protection of the intermediate primary hydroxyl as its TBS–ether provided **37** in 67% overall yield (Scheme 13). It was now necessary to reduce the diester moiety to install the requisite *gem*-dimethyl moiety. Although treatment of **37** with DIBALH in toluene did reduce the methyl esters to generate the expected 1,3-diol, some silyl deprotection also occurred. However, reduction of **37** with $LiAlH_4$ gave the desired 1,3-diol in 91% yield. Subsequent treatment with methanesulfonyl chloride (MsCl) and Et_3N provided bismesylate **38** in 79% yield.



Scheme 13.

Initial attempts to reduce the bismesylate functionality in **38** to provide the *gem*-dimethyl moiety were performed utilizing $LiAlH_4$. Unfortunately, the reaction was somewhat recalcitrant and failed to proceed to completion. Partially reduced monomesylate was recovered, even after extended reaction times (>24 h). Ultimately, **38** was cleanly reduced using $LiBHEt_3$ to give the desired *gem*-dimethyl intermediate that was treated with TBAF in THF to deliver **39** in 70% overall yield for the two steps. When **39** was subjected to heterogeneous catalytic hydrogenation in the presence of base-washed palladium on carbon under H_2 (1 atm), stereo- and chemoselective reduction of the trisubstituted olefin ensued with concomitant removal of the benzyl protecting group to provide tremulenediol A (**4**) in 82% yield as the only isolable product. The spectral data (e.g., 500 MHz ^1H and 125 MHz ^{13}C NMR and IR) and optical rotation for synthetic **4** were consistent with those reported in the literature.[1] Subsequent treatment of **4** with MnO_2 provided tremulenolide A (**3**), which also exhibited spectral characteristics (e.g., 500 MHz ^1H and 125 MHz ^{13}C NMR) and optical rotation consistent with those reported in the literature.[1]

3. Conclusions

In summary, concise, enantioselective syntheses of tremulenediol A (**4**) and tremulenolide A (**3**), two representative sesquiterpene metabolites of the tremulane class, have been achieved. The synthetic route is highlighted by a chiral

rhodium(II)-catalyzed cyclopropanation to establish the requisite absolute stereochemistry. A transition metal-catalyzed allylic alkylation is then utilized to assemble the complete carbon ensemble present in the natural products and set the stage for a diastereoselective rhodium(I)-catalyzed [5+2] intramolecular cycloaddition. These studies led to the discovery and development of a novel $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation reaction that generally proceeds with a unique regioselective outcome for structurally different substrates. This allylic alkylation has been coupled in tandem with a number of different $[Rh(CO)_2Cl]_2$-catalyzed carbocyclizations, including [5+2] cycloadditions, to enable rapid access to complex cyclic carboskeletal frameworks. The trio of transition metal-catalyzed operations described herein results in a convergent and highly efficient enantioselective entry to **3** and **4** as evidenced by their synthesis in 6% (16 steps) and 5.2% (17 steps) overall yields, respectively. Other applications of these and other sequential and domino transition metal-catalyzed reactions are in progress and will be reported in due course.

4. Experimental

4.1. General

Solvents and reagents were reagent-grade and used without purification unless otherwise noted. Dichloromethane (CH_2Cl_2), triethylamine (Et_3N), and diisopropylamine were distilled from calcium hydride and stored under nitrogen. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were passed through a column of neutral alumina and stored under argon. Methanol (MeOH) and dimethylformamide (DMF) were passed through a column of molecular sieves and stored under argon. Toluene was passed through a column of Q5 reactant and stored under argon. All reactions were done in flame-dried glassware under nitrogen unless otherwise indicated. ^{1}H nuclear magnetic resonance (NMR) spectra were obtained at either 500, 400 or 300 MHz as solutions in $CDCl_3$. ^{13}C NMR were obtained at either 125, 100 or 75 MHz as solutions in $CDCl_3$. Chemical shifts are reported in parts per million (ppm, δ), and referenced from tetramethylsilane. Coupling constants are reported in hertz (Hz). Spectral splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; comp, complex; and br, broad. Infrared (IR) spectra were obtained using a Perkin–Elmer FTIR 1600 spectrophotometer using sodium chloride plates as indicated, and reported as wave numbers. Low-resolution chemical ionization mass spectra were obtained with a Finnigan TSQ-70 instrument. High-resolution measurements were made with a VG Analytical ZAB2-E instrument. Analytical thin layer chromatography was performed using Merck 250 micron 60F-254 silica gel plates. The plates were visualized with UV light, ninhydrin, phosphomolybdic acid, *p*-anisaldehyde, and potassium permanganate. Flash column chromatography was performed according to Still's procedure[24] using ICN Silitech 32-63 D 60A silica gel.

4.1.1. 3-Methylpenta-1,4-dien-3-yl acetoacetate (16). A solution of freshly distilled diketene (1.048 g, 12.5 mmol) in THF (2 mL) was added dropwise to a stirred mixture of *N*,*N*-dimethylaminopyridine (DMAP) (152 mg, 1.25 mmol), sodium acetate (102 mg, 1.25 mmol), and **15**[13] (610 mg, 6.23 mmol) in THF (18 mL) at −10 °C. The reaction mixture was allowed to warm to room temperature by removal of the cooling bath and stirred for 5.5 h. Satd aq NaCl (20 mL) and Et_2O (20 mL) were added, and the layers were separated. The aqueous phase was extracted with Et_2O (2×20 mL), and the combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by Kugelrohr distillation (55–57 °C, 0.1 mmHg) to yield 1.052 g (93%) of **16** as a colorless oil: ^{1}H NMR (300 MHz) δ 6.08 (dd, J=17.4, 10.8 Hz, 2H), 5.20 (m, 4H), 3.38 (s, 2H), 2.23 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (65 MHz) δ 200.7, 165.6, 139.7, 114.7, 83.3, 51.0, 30.1, 23.9; IR ($CHCl_3$) 2987, 1744, 1720, 1642, 1410, 1361, 1318, 1269, 1149, 997, 932 cm^{-1}; mass spectrum (CI) *m*/*z* 183.1028 [$C_{10}H_{15}O_3$ (M+1) requires 183.1021], 165, 161, 159, 139, 135, 121, 103 (base).

4.1.2. 3-Methylpenta-1,4-dien-3-yl diazoacetate (9). A solution of *p*-toluenesulfonyl azide (826 mg, 4.28 mmol) (synthesized from *p*-toluenesulfonyl chloride and sodium azide) in CH_3CN (6 mL) was added to a stirred solution of **16** (648 mg, 3.57 mmol) and Et_3N (0.75 mL, 5.35 mmol) in CH_3CN (30 mL) at room temperature. The reaction mixture was stirred for 4 h, whereupon a solution of $LiOH\cdot H_2O$ (449 mg, 10.7 mmol) in H_2O (3.5 mL) was added, and the reaction mixture was stirred for an additional 4 h. The mixture was diluted with water (30 mL) and extracted with Et_2O (3×30 mL). The combined organic fractions were washed with satd aq NaCl (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with pentane/Et_2O (10:1) to give 573 mg (97%) of **9** as a yellow oil: ^{1}H NMR (300 MHz) δ 6.08 (dd, J=17.5, 10.7 Hz, 2H), 5.23 (d, J=17.5 Hz, 2H), 5.18 (d, J=10.7 Hz, 2H), 4.69 (br s, 1H), 1.65 (s, 3H); ^{13}C NMR (65 MHz) δ 171.0, 140.2, 131.8, 114.1, 82.6, 20.8; IR ($CHCl_3$) 3033, 2985, 2109, 1694, 1371, 1248, 1186, 1092, 992, 924, 740 cm^{-1}; mass spectrum (CI) *m*/*z* 167.0821 [$C_8H_{11}N_2O_2$ (M+1) requires 167.0821], 166 (base), 143, 142.

4.1.3. [1*S*-(1β,5α)]-4-Methyl-4-vinyl-3-oxabicyclo[3.1.0]-hexan-2-one (8). A solution of **9** (23 mg, 0.137 mmol) in CH_2Cl_2 (7 mL) was added to a refluxing solution of $Rh_2[5(R)\text{-MEPY}]_4$ (13 mg, 13.7 μmol) in CH_2Cl_2 (114 mL) over 17 h using a syringe pump. The resulting mixture was heated under reflux for 4 h and then allowed to cool to room temperature. The mixture was concentrated under reduced pressure and a crude ^{1}H NMR spectra indicated a mixture (1:1) of *endo* and *exo* isomers. The crude residue was purified by flash chromatography eluting with pentane/Et_2O (1:1) to give 19 mg (99%) of **8** as a clear, colorless oil (combined mass of both isomers isolated). *Isomer A*: ^{1}H NMR (300 MHz) δ 5.98 (dd, J=17.2, 10.7 Hz, 1H), 5.37 (d, J=17.2 Hz, 1H), 5.18 (d, J=10.7 Hz, 1H), 2.16–2.04 (m, 2H), 1.44 (s, 3H), 1.17 (ddd, J=8.8, 7.6, 5.0 Hz, 1H), 1.00 (dt, J=5.0, 3.2 Hz, 1H); ^{13}C NMR (65 MHz) δ 174.3, 133.0, 119.0, 66.7, 31.6, 29.8, 28.3, 21.5; IR ($CHCl_3$) 2987, 1769, 1453, 1413, 1313, 1248, 1196, 1044, 959, 838 cm^{-1}; mass spectrum (CI) *m*/*z* 139.0764 [$C_8H_{11}O_2$ (M+1) requires 139.0759], 139 (base). *Isomer B*: ^{1}H NMR (300 MHz) δ 5.85 (dd, J=17.3, 10.9 Hz, 1H), 5.27 (dd, J=17.3, 1.0 Hz, 1H), 5.15 (dd, J=10.9, 1.0 Hz, 1H), 2.21–2.04 (m, 2H), 1.55 (s, 3H), 1.14 (ddd, J=8.8, 7.6, 4.9 Hz, 1H), 0.88 (dt, J=4.9, 3.4 Hz, 1H).

4.1.4. 2-((1*R*,2S)-2-(Hydroxydiphenylmethyl)cyclopropyl)but-3-en-2-ol. A 1.0 M solution of PhLi in THF (0.58 mL, 0.58 mmol) was added to a stirred solution of **8** (20 mg, 0.14 mmol) in THF (1.5 mL) at 0 °C, the cooling bath was removed, and the mixture was stirred for 1.5 h. It was then cooled to 0 °C, and satd aq $NaHCO_3$ (2 mL) was added. The layers were separated, and the aqueous phase was extracted with Et_2O (3×2 mL). The organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (2:1) to give 38 mg (92%) of the target ketone as a mixture (1:1) of diastereomers as a clear, colorless oil: ^{1}H NMR (500 MHz) δ 7.69–7.66 (comp, 2H), 7.42–7.39 (comp, 2H), 7.38–7.31 (comp, 2H), 7.28–7.23 (comp, 3H), 7.17 (app tt, J=7.5, 1.5 Hz, 1H), 6.02 (dd, J=17.5, 11.0 Hz, 1H), 5.19 (dd, J=17.5, 1.0 Hz, 1H), 5.02 (dd, J=11.0, 1.0 Hz, 1H), 1.98 (ddd, J=16.5, 9.0, 7.0 Hz, 1H), 1.23 (ddd, J=12.5, 7.5, 5.0 Hz, 1H), 1.11 (ddd, J=16.5, 9.0, 7.5 Hz, 1H), 0.95 (s, 3H), 0.80 (ddd, J=14.0, 9.0, 5.0 Hz, 1H); ^{13}C NMR (125 MHz) δ 149.3, 149.0, 145.5, 127.8, 127.8, 126.8, 126.7, 126.6, 126.2, 111.3, 75.2, 72.0, 30.8, 28.7, 28.4, 3.11; IR (CH_2Cl_2) 3585, 3366, 3003, 1598, 1491, 1448, 1185, 1062, 924 cm^{-1}; mass spectrum (CI) *m/z* 239.1499 [$C_{20}H_{21}O_2$ (M+1) requires 239.1541], 277 (base), 259, 199, 193; HPLC (Chiralcel AD column, hexanes/isopropanol 98:2, flow=0.5 mL/min, t_R=60.8, 62.7, 73.1, 78.1 min).

4.1.5. (2*S*,3*S*)-(2-(1,4,4-Trimethylpent-1-enyl)cyclopropanecarboxylic acid (17). A 1.40 M solution of *t*-BuLi in pentane (0.31 mL, 0.43 mmol) was added to a solution of CuCN (20 mg, 0.22 mmol) in degassed THF (1 mL) at −78 °C, and the resulting slurry was allowed to warm slowly to 0 °C with stirring (app 10 min). This yellow solution was then transferred via cannula to a solution of **8** (20 mg, 0.14 mmol) in degassed THF (0.5 mL) at 0 °C, the solution was allowed to warm to room temperature by removal of the cooling bath and stirred for 4 h. The mixture was then cooled to 0 °C and satd aq NH_4Cl/NH_4OH (9:1, 2 mL) was added. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3×2 mL), the combined organic fractions were dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (2:1) to give 22 mg (80%) of **17** as a mixture (2.3:1) of *trans* and *cis* isomers as a clear, colorless oil: *trans isomer*: ^{1}H NMR (400 MHz) δ 5.43–5.40 (m, 1H), 2.06–1.79 (m, 4H), 1.62 (d, J= 0.7 Hz, 3H), 1.43 (app dt, J=7.8, 5.2 Hz, 1H), 1.11 (ddd, J=12.4, 7.6, 4.8 Hz, 1H), 0.86 (s, 9H); ^{13}C NMR (100 MHz) δ 177.9, 130.1, 126.0, 41.8, 31.7, 30.7, 29.2, 19.6, 17.1, 12.0; IR ($CHCl_3$) 3689, 3022, 1602, 1226 cm^{-1}; mass spectrum (CI) *m/z* 197.1543 [$C_{12}H_{21}O_2$ (M+1) requires 197.1542], 393, 197 (base), 179, 151, 141, 125.

4.1.6. 6-Benzyloxy-2-methyl-4-hexyn-2-ol (19). A 1.9 M solution of *n*-BuLi in hexanes (1.1 mL, 2.0 mmol) was added to a stirred solution of protected propargyl alcohol **18** (292 mg, 2.0 mmol) in THF (2.5 mL) at −78 °C, and the resulting yellow solution was stirred for 1 h. To a solution of isobutylene oxide (72.1 mg, 0.089 mL, 1 mmol) in THF (2.5 mL), freshly distilled $BF_3\cdot OEt_2$ (283 mg, 0.25 mL, 2 mmol) was added and the reaction mixture was stirred for 7 h at −78 °C. The solution was allowed to warm to room temperature by removal of the cooling bath and stirred for an additional 40 min. Satd aq $NaHCO_3$ (5 mL) was added, and the layers were separated. The aqueous phase was extracted with Et_2O (3×5 mL), and the combined organic fractions were washed with satd aq NaCl (5 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to give 218 mg (~100%) of **19** as a clear, yellow oil: ^{1}H NMR (400 MHz) δ 7.34–7.25 (m, 5H), 4.58 (s, 2H), 4.18 (t, J=2.0 Hz, 2H), 2.42 (t, J=2.0 Hz, 2H), 2.29 (br s, 1H), 1.31 (s, 6H); ^{13}C NMR (100 MHz) δ 137.2, 128.2, 127.8, 127.6, 83.5, 78.7, 71.4, 69.9, 57.5, 34.4, 28.7; IR (Neat) 3416, 3031, 2973, 2930, 2858, 2282, 2220, 1496, 1454 cm^{-1}; mass spectrum (CI) *m/z* 219.1374 [$C_{14}H_{19}O_2$ (M+1) requires 219.1385], 237, 219, 183, 171 (base), 161, 143.

4.1.7. 6-Benzyloxy-2-bromo-2-methyl-4-hexyne (20). Trimethylsilyl bromide (0.12 mL, 0.916 mmol) was added to a solution of **19** (50 mg, 0.229 mmol) in CH_2Cl_2 (3 mL) at room temperature, and the reaction mixture was stirred for 4 h. The mixture was warmed to 50 °C (bath temperature), stirred for an additional 2 h, and allowed to cool to room temperature by removal of the cooling bath. The reaction mixture was diluted with satd aq $NaHCO_3$ (3 mL), and the layers were separated. The aqueous phase was extracted with Et_2O (3×12 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (20:1) to give 15 mg (23%) of **20** as a clear, colorless oil: ^{1}H NMR (400 MHz) δ 7.38–7.26 (m, 5H), 4.61 (s, 2H), 4.19 (t, J=2.0 Hz, 2H), 2.86 (t, J=2.0 Hz, 2H), 1.85 (s, 6H); ^{13}C NMR (100 MHz) δ 137.2, 128.3, 128.0, 127.7, 83.1, 78.9, 71.3, 62.4, 57.4, 38.3, 33.6; IR ($CDCl_3$) 2969, 2926, 2859, 2259, 1721, 1453, 1371, 1264, 1107, 1070, 707 cm^{-1}; mass spectrum (CI) *m/z* 279.0378 [$C_{14}H_{16}O_1Br$ (M−1) requires 279.0384], 281, 279, 265, 263, 201, 183, 171 (base).

4.1.8. 4-Benzyloxy-2-butyn-1-ol (25). NaH (2.326 g of a 60% mineral oil suspension, 58.0 mmol) was added portion wise to a solution of 2-butyn-1,4-diol (**24**) (10.0 g, 116.3 mmol) in DMF (250 mL) at 0 °C. The resulting mixture was stirred for 30 min, whereupon TBAI (2.148 g, 5.8 mmol) and benzyl bromide (6.9 mL, 58.0 mmol) were added and the reaction mixture allowed to warm to room temperature by removal of the cooling bath and stirred for an additional 2 h. H_2O (200 mL) and 10% HCl (200 mL) were added, and the layers separated. The aqueous phase was extracted with Et_2O (3×200 mL), and the combined organic fractions were dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to give 5.460 g (53%) of **25** as a clear, yellow oil. ^{1}H NMR (500 MHz) δ 7.35–7.27 (comp, 5H), 4.57 (s, 2H), 4.30 (t, J=1.8 Hz, 2H), 4.19 (t, J=1.8 Hz, 2H), 1.82 (br s, 1H); ^{13}C NMR (65 MHz) δ 137.1, 128.4, 128.0, 127.8, 84.7, 81.6, 71.7, 57.3, 51.0; mass spectrum (CI) *m/z* 176 (base), 154, 146.

4.1.9. 2-(4-Benzyloxy-2-butynyl)malonic acid dimethyl ester (23). Dimethyl malonate (2.58 mL, 22.6 mmol) was added to a suspension of NaH (542 mg of a 60% mineral

oil suspension, 13.5 mmol) in THF (15 mL) at 0 °C, and the mixture was stirred for 25 min. A solution of **26** (1.147 g, 4.51 mmol) in THF (5 mL) was then added via syringe, and the reaction mixture was allowed to warm to room temperature and stirred for an additional 2.5 h. The mixture was cooled to 0 °C, H_2O (20 mL) was added, and the layers were separated. The aqueous phase was extracted with Et_2O (3×20 mL), and the combined organic fractions were dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (2:1) to give 1.269 g (97%) of **23** as a clear, colorless oil: ^{1}H NMR (500 MHz) δ 7.33–7.25 (comp, 5H), 4.53 (s, 2H), 4.10 (t, J=2.1 Hz, 2H), 3.74 (s, 6H), 3.60 (t, J=7.6 Hz, 1H), 2.84 (dt, J=7.5, 2.1 Hz, 2H); ^{13}C NMR (65 MHz) δ 168.3, 137.3, 128.3, 128.0, 127.7, 82.4, 79.4, 71.1, 57.2, 52.7, 23.9; IR (Neat) 3031, 2954, 2853, 1738, 1454, 1345, 1071 cm^{-1}; mass spectrum (CI) m/z 291.1232 [$C_{16}H_{19}O_5$ (M+1) requires 291.1230], 261, 183.

4.1.10. 2-(4-Benzyloxybut-2-ynyl)-2-[3-(2*S*,3*S*)-(2-carboxycyclopropyl)but-2-enyl]malonic acid dimethyl ester (27). $Pd(PPh_3)_4$ (81 mg, 73 μmol) and PPh_3 (190 mg, 0.725 mmol) were added sequentially to a solution of **8** (100 mg, 0.725 mmol) in degassed THF (4 mL) at room temperature, and the resulting solution was stirred for 20 min. In a separate flask, **23** (462 mg, 1.59 mmol) was added to a slurry of NaH (58 mg of a 60% mineral oil suspension, 1.45 mmol) in degassed THF (4 mL) at room temperature. After stirring for 20 min at room temperature, the resulting homogeneous solution was transferred via cannula to the flask containing the catalyst and substrate. The mixture was heated under reflux for 4 h. The resulting dark brown solution was allowed to cool to room temperature by removal of the oil bath and then cooled to 0 °C. Aq 1 M $NaHSO_4$ (8 mL) was added, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic fractions were washed with satd aq NaCl (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (2:1–1:1) to give 220 mg (71%) of **27** as a clear, yellow oil: ^{1}H NMR (500 MHz) δ 7.35–7.27 (comp, 5H), 5.13 (t, J=7.4, 1.5 Hz, 1H), 4.57 (s, 2H), 4.07 (t, J=1.0 Hz, 6H), 3.68 (s, 3H), 3.66 (s, 3H), 2.83 (br s, 2H, C9-H), 2.81 (br s, 2H, C7-H), 1.95 (br q, J=16.2, 8.1 Hz, 1H), 1.81 (m, 1H), 1.70 (s, 3H), 1.36 (m, 1H), 1.10 (m, 1H); ^{13}C NMR (125 MHz) δ 175.9, 170.5, 137.5, 128.4, 128.2, 127.8, 127.8, 121.1, 82.0, 78.8, 71.2, 57.1, 52.7, 30.7, 29.7, 22.8, 19.6, 17.3, 17.3; IR ($CDCl_3$) 2952, 2259, 1735, 1698, 1436, 1291, 1211, 1070 cm^{-1}; mass spectrum (CI) m/z 429.1907 [$C_{16}H_{19}O_5$ (M+1) requires 429.1913], 399, 321, 279.

4.1.11. 2-(4-Benzyloxybut-2-ynyl)-2-[3-(2*S*,4*S*)-(2-formylcyclopropyl)but-2-enyl]malonic acid dimethyl ester (35). Oxalyl chloride (50 μL, 0.485 mmol) was added dropwise to a solution of **27** (104 mg, 0.242 mmol) and DMF (five drops) in CH_2Cl_2 (2.5 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature by removal of the cooling bath and then stirred for 3 h. The mixture was concentrated under reduced pressure, and the crude acid chloride was dissolved in THF (2 mL). The solution was cooled to −78 °C, and a slurry of $LiAlH(O^tBu)_3$ (124 mg, 0.485 mmol) in THF (0.5 mL) was added. The reaction mixture was stirred at −78 °C for 1 h. Aq 1 M HCl (2 mL) was added, and the mixture allowed to warm to room temperature by removal of the cooling bath, and then the layers were separated. The aqueous phase was extracted with EtOAc (3×2 mL), and the combined organic fractions were then dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to give 84 mg (84%) of **35** as a clear, colorless oil: ^{1}H NMR (300 MHz) δ 8.74 (d, J=6.9 Hz, 1H), 7.36–7.28 (comp, 5H), 5.31 (t, J=7.8 Hz, 1H), 4.55 (s, 2H), 4.13 (t, J=2.1 Hz, 2H), 3.74 (s, 3H), 3.73 (s, 3H), 2.91–2.83 (comp, 4H), 2.11 (app dt, J=15.9, 8.1 Hz, 1H), 1.86 (app ddt, J=12.0, 7.8, 4.8 Hz, 1H), 1.72 (s, 3H), 1.59 (app dt, J=7.2, 5.1 Hz, 1H), 1.33 (app dt, J=7.8, 5.4 Hz, 1H); ^{13}C NMR (75 MHz) δ 201.7, 170.3, 137.5, 134.9, 128.1, 127.8, 121.1, 81.3, 79.3, 71.2, 57.3, 56.9, 52.8, 30.6, 30.2, 28.3, 23.2, 17.8, 11.8; IR ($CDCl_3$) 2953, 2853, 2256, 1736, 1697, 1437, 1292, 1208, 1069 cm^{-1}; mass spectrum (CI) m/z 413.1959 [$C_{24}H_{29}O_6$ (M+1) requires 413.1964], 413 (base), 305, 245.

4.1.12. (3a*S*,7*S*)-8-Benzyloxymethyl-7-formyl-4-methyl-3,3a,6,7-tetrahydro-1*H*-azulene-2,2-dicarboxylic acid dimethyl ester (36). $[Rh(CO)_2Cl]_2$ (2 mg, 4.8 μmol) was dissolved in degassed toluene (2 mL), and a solution of **35** (20 mg, 0.048 mmol) in degassed toluene (5 mL) was added. The resulting mixture was heated for 30 min at 110 °C (bath temperature). The mixture was allowed to cool to room temperature by removal of the oil bath, and then filtered through a short plug of neutral alumina. The filtrate was concentrated under reduced pressure, and the crude residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to give 17 mg (85%) of **36** as a clear, colorless oil: ^{1}H NMR (500 MHz) δ 9.59 (s, 1H), 7.36–7.27 (comp, 5H), 5.51–5.49 (m, 1H), 4.51 (d, J=11.6 Hz, 1H), 4.46 (d, J=11.8 Hz, 1H), 4.01 (app dt, J=12.1, 1.2 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.37 (br s, 1H), 3.23 (dd, J=17.3, 2.0 Hz, 1H), 3.20 (t, J=6.0 Hz, 1H), 2.89 (dd, J=16.7, 1.4 Hz, 1H), 2.73 (ddd, J=12.4, 7.4, 2.0 Hz, 1H), 2.68–2.59 (m, 1H), 2.35–2.29 (m, 1H), 2.07 (t, J=12.7 Hz, 1H), 1.68 (d, J=0.6 Hz, 1H); ^{13}C NMR (125 MHz) δ 200.4, 171.7, 171.4, 142.5, 138.2, 134.3, 128.4, 127.7, 127.6, 122.8, 71.9, 71.2, 57.3, 52.9, 52.8, 51.7, 44.5, 39.3, 39.3, 26.4, 24.2; IR ($CDCl_3$) 3022, 2954, 1732, 1698, 1436, 1374, 1291, 1211, 1071 cm^{-1}; mass spectrum (CI) m/z 413.1956 [$C_{24}H_{29}O_6$ (M+1)], 413, 305 (base), 273, 245.

4.1.13. [2*S*,3*S*]-8-Benzyloxymethyl-7-hydroxymethyl-4-methyl-3,3a,6,7-tetrahydro-1*H*-azulene-2,2-dicarboxylic acid dimethyl ester. $NaBH_4$ (2 mg, 0.029 mmol) was added in one portion to a solution of **36** (6 mg, 0.014 mmol) in THF (1 mL) at 0 °C, and the mixture was stirred for 1 h 15 min. Satd aq NH_4Cl (1 mL) was added and the layers were separated. The aqueous phase was extracted with EtOAc (3×1 mL), and the combined organic fractions were dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to give 5 mg (83%) of the primary alcohol as a clear, colorless oil: ^{1}H NMR (500 MHz) δ 7.35–7.27 (comp, 5H), 5.50–5.48 (m, 1H), 4.53 (s, 2H), 4.03 (d, J=10.0 Hz, 1H), 3.79 (d, J=10.0 Hz, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.69 (dd, J=13.9, 5.2 Hz, 1H), 3.64 (dd, J=10.6, 6.0 Hz, 1H), 3.60–3.55 (m, 1H), 3.17 (br d,

J=16.7 Hz, 1H), 2.95–2.92 (m, 1H), 2.75 (ddd, J=12.4, 7.4, 2.0 Hz, 1H), 2.42–2.35 (m, 2H), 2.28–2.20 (comp, 2H), 2.04 (t, J=12.6 Hz, 1H), 1.71 (s, 3H); ^{13}C NMR (125 MHz) δ 171.9, 171.7, 141.8, 137.9, 135.2, 130.7, 128.4, 127.8, 127.7, 123.2, 72.7, 72.2, 64.1, 57.0, 52.9, 52.8, 45.2, 42.9, 39.4, 39.2, 29.0, 23.8; IR ($CHCl_3$) 3468, 3015, 2954, 1731, 1436, 1273, 1201, 1060 cm^{-1}; mass spectrum (CI) m/z 415.2124 [$C_{25}H_{31}O_6$ (M+1) requires 415.2121], 415, 307 (base), 207, 247.

4.1.14. (3a*S*,4*Z*,7*S*,8*E*)-Dimethyl 8-((benzyloxy)methyl)-3,3a,6,7-tetrahydro-7-[(*t*-butyldimethylsiloxy)methyl]-4-methylazulene-2,2(1*H*)-dicarboxylate (37). TBSCl (24 mg, 0.16 mmol) was added in one portion to a solution of imidazole (11 mg, 0.16 mmol) and the alcohol from the preceding experiment (32 mg, 78.0 μmol) in DMF (2 mL) at room temperature, and the reaction mixture was stirred for 4 h. Satd aq NaCl (1 mL) was added, and the layers were separated. The aqueous phase was extracted with Et_2O (3×1 mL), and the combined organic fractions were dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexane/EtOAc (2:1) to provide 33 mg (81%) of **37** as a clear, colorless oil: ^{1}H NMR (500 MHz) δ 7.32–7.31 (comp, 5H), 5.42–5.41 (m, 1H), 4.47 (d, J=12.0 Hz, 1H), 4.42 (d, J=12.0 Hz, 1H), 3.96 (d, J=10.0 Hz, 1H), 3.95 (d, J=10.0 Hz, 1H), 3.72 (s, 3H), 3.71 (s, 3H), 3.64 (app t, J=9.5 Hz, 1H), 3.59 (dd, J=9.5, 5.5 Hz, 1H), 3.37–3.36 (m, 1H), 3.10 (d, J=17.0 Hz, 1H), 2.96 (dd, J=17.5, 2.5 Hz, 1H), 2.54 (m, 1H), 2.35–2.31 (m, 1H), 2.27–2.23 (m, 1H), 1.96 (app t, J=13.0 Hz, 1H), 1.70 (d, J=1.0 Hz, 3H), 0.84 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (125 MHz) δ 171.9, 171.9, 138.8, 138.4, 133.2, 131.9, 128.3, 127.6, 127.4, 123.4, 72.4, 71.8, 62.6, 57.4, 56.7, 52.7, 46.5, 41.7, 39.1, 25.8, 25.6, 17.9, −3.7; mass spectrum (CI) m/z 529.2957 [$C_{30}H_{45}O_6Si$ (M+1) requires 529.2985], 529, 421, 289 (base), 275.

4.1.15. (3a*S*,4*Z*,7*S*,8*E*)-Dimethyl 8-((benzyloxy)methyl)-3,3a,6,7-tetrahydro-7-[(*t*-butyldimethylsiloxy)methyl]-4-methylazulene-2,2(1*H*)-diol. $LiAlH_4$ (21 mg, 0.55 mmol) was added to a stirred solution of diester **20** (145 mg, 0.27 mmol) in THF (3 mL) at 0 °C. The reaction mixture was allowed to warm slowly to room temperature and stirred for 4 h. The mixture was then cooled to 0 °C, and satd aq potassium sodium tartrate (3 mL) was added, and the mixture was stirred for 30 min at room temperature. The layers were separated, and the aqueous phase was extracted with EtOAc (5×5 mL). The combined organic fractions were washed with satd aq NaCl (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure to yield 120 mg (91%) of diol as an opaque, colorless oil: ^{1}H NMR (500 MHz) δ 7.34–7.28 (comp, 5H), 5.42–5.40 (m, 1H), 4.49 (d, J=11.6 Hz, 1H), 4.44 (d, J=11.6 Hz, 1H), 3.97 (d, J=10.4 Hz, 1H), 3.95 (d, J=10.4 Hz, 1H), 3.71 (d, J=9.2 Hz, 1H), 3.65 (d, J=9.2 Hz, 1H), 3.74–3.57 (comp, 4H), 3.43–3.38 (m, 1H), 2.55–2.52 (m, 1H), 2.41–2.16 (comp, 6H), 1.71 (s, 3H), 0.88 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (125 MHz) δ 141.8, 138.5, 134.8, 131.5, 128.3, 127.8, 127.6, 122.7, 72.8, 72.1, 71.1, 67.4, 62.9, 45.7, 45.3, 44.5, 42.4, 42.2, 37.6, 37.5, 35.9, 18.3, −5.4, −5.4; mass spectrum (CI) m/z 473.3063 [$C_{28}H_{45}O_4Si$ (M+1) requires 473.3087], 473, 365, 233, 215 (base).

4.1.16. ((3a*S*,4*Z*,7*S*,8*E*)-8-(Benzyloxymethyl)-7-((*tert*-butyldimethylsilyloxy)methyl)-2-methanesulfonyloxymethyl-4-methyl-1,2,3,3a,6,7-hexahydroazulen-2-yl)-methyl methanesulfonate (38). Methanesulfonyl chloride (291 mg, 0.20 mL, 2.50 mmol) was added dropwise to a stirred solution of the diol from the preceding experiment (120 mg, 0.25 mmol) and Et_3N (257 mg, 0.35 mL, 2.50 mmol) in CH_2Cl_2 (5 mL) at 0 °C, and the resultant mixture was stirred for 3 h. Satd aq $NaHCO_3$ (5 mL) was added, and the layers were separated. The aqueous phase was extracted with Et_2O (3×5 mL), and the combined organic fractions were dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 137 mg (79%) of **38** as a clear, colorless oil: ^{1}H NMR (500 MHz) δ 7.37–7.28 (comp, 5H), 5.48–5.44 (m, 1H), 4.49 (d, J=11.6 Hz, 1H), 4.44 (d, J=11.6 Hz, 1H), 4.21–4.06 (comp, 2H), 4.16 (d, J=9.6 Hz, 1H), 4.08 (d, J=9.6 Hz, 1H), 3.92 (br s, 1H), 3.70–3.62 (comp, 2H), 3.51–3.44 (m, 1H), 3.03 (s, 3H), 3.03 (s, 3H), 2.54–2.53 (m, 1H), 2.42–2.25 (comp, 3H), 2.17 (dd, J=13.2, 8.0 Hz, 1H), 1.70 (s, 3H), 0.88 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (125 MHz) δ 138.8, 138.2, 133.9, 133.1, 128.2, 127.6, 127.5, 123.4, 72.5, 72.3, 72.3, 72.1, 69.1, 62.7, 42.8, 37.2, 37.1, 36.6, 36.6, 31.4, 25.8, 24.3, 18.1, −5.1, −5.2; IR ($CDCl_3$) 3100, 3031, 2929, 2856, 2260, 1730, 1469, 1362, 1255, 1178, 1094, 978, 850, 778, 527; mass spectrum (CI) m/z 629.2627 [$C_{30}H_{49}O_8SiS_2$ (M+1) requires 629.2638], 629, 557, 555 (base).

4.1.17. [(3a*E*,5*S*,7*Z*,8a*S*)-4-(Benzyloxymethyl)-2,2,8-trimethyl-1,2,3,5,6,8a-hexahydroazulen-5-yl]methanol (39). A 1.0 M solution of $LiBHEt_3$ (0.71 mL, 0.71 mmol) in THF was added to a solution of **38** (56 mg, 0.08 mmol) in THF (2 mL) at room temperature, and the mixture was stirred for 8 h. The reaction mixture was then cooled to 0 °C, 1 M HCl (2 mL) was added, and the mixture was allowed to warm to room temperature. The layers were separated, and the aqueous phase was extracted with EtOAc (5×5 mL). The combined organic fractions were washed with satd aq NaCl (mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was then dissolved in THF (1.7 mL), and a solution of TBAF (85 mg, 0.27 mmol) in THF (0.3 mL) was added at room temperature. The reaction was stirred for 3 h and then satd aq NaCl (5 mL) was added, and the layers were separated. The aqueous phase was extracted with EtOAc (5×5 mL), the combined organic fractions were dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 20 mg (70%) of **39** as a clear, colorless oil: ^{1}H NMR (500 MHz) δ 7.38–7.27 (comp, 5H), 5.49–5.44 (m, 1H), 4.52 (s, 1H), 4.01 (d, J=9.6 Hz, 1H), 3.75–3.68 (comp, 3H), 2.51 (app t, J=6.0 Hz, 1H), 2.47–2.78 (comp, 2H), 2.25 (dd, J=16.0, 2.0 Hz, 1H), 2.20–2.18 (m, 1H), 2.13 (d, J=16.0 Hz, 1H), 1.76 (ddd, J=11.6, 7.6, 2.0 Hz, 1H), 1.68 (s, 3H), 1.51 (app t, J=12.0 Hz, 1H), 1.07 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (125 MHz) δ 147.2, 138.1, 137.2, 129.2, 128.4, 127.8, 127.7, 122.5, 72.7, 72.5, 64.3, 47.0, 46.0, 44.8, 43.3, 35.4, 29.4, 29.3, 26.8, 23.9; IR ($CDCl_3$) 2955, 2247, 1602, 1454, 1365, 1307, 1058; mass spectrum (CI) m/z 325.2171 [$C_{22}H_{29}O_2$ (M+1) requires 325.2168], 327, 323, 295, 247, 219 (base).

4.1.18. Tremulenediol A (4). Palladium on carbon (10 wt %, 1 mg) was added to a solution of **39** (5 mg, 15.3 μmol) in MeOH (0.1 mL) at room temperature. The atmosphere in the flask was then replaced with H_2 (1 atm) and the mixture was stirred under an atmosphere of H_2 (balloon) for 3 d. The reaction mixture was then filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (1:1) to provide 3 mg (82%) of **4** as a clear, colorless oil; $[\alpha]_D^{25}$ +40.0 (*c* 0.24, MeOH) [lit.[1] $[\alpha]_D$ +41.7 (*c* 0.24, MeOH)]. Spectra were consistent with literature data:[1] ^{1}H NMR (500 MHz) δ 4.25 (d, J=11.0 Hz, 1H), 4.02 (app t, J=9.5 Hz, 1H), 3.84 (dt, J=11.0, 1.5 Hz, 1H), 3.62 (dd, J=9.5, 5.0 Hz, 1H), 3.10 (br t, J=8.5 Hz, 1H), 2.57–2.54 (m, 1H), 2.29 (dd, J=15.5, 2.5 Hz, 1H), 1.93 (br d, J=15.0 Hz, 1H), 1.84–1.81 (m, 1H), 1.80 (br d, J=11.5 Hz, 1H), 1.79–1.74 (m, 1H), 1.61 (dd, J=12.5, 3.0 Hz, 1H), 1.59–1.58 (m, 1H), 1.54–1.51 (m, 1H), 1.38 (br d, J=12.0 Hz, 1H), 1.07 (s, 3H), 0.87 (s, 3H), 0.82 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz) δ 145.8, 132.4, 65.8, 63.3, 48.0, 46.0, 45.5, 45.4, 37.0, 32.6, 31.6, 28.5, 26.9, 22.5, 11.6.

4.1.19. Tremulenolide A (3). MnO_2 (3.0 mg, 33.0 μmol) was added to a solution of **4** (4.0 mg, 16.0 μmol) in CH_2Cl_2 (1 mL) at room temperature. The resulting mixture was stirred for 24 h, filtered through a short plug of silica gel, and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (5:1) to provide 3.4 mg (86%) of **3** as a clear, colorless oil; $[\alpha]_D^{25}$ +99.6 (*c* 0.24, MeOH) [lit.[1] $[\alpha]_D$ +110.7 (*c* 0.14, MeOH)]. Spectra results were consistent with literature data:[1] ^{1}H NMR (500 MHz) δ 4.35 (app t, J=8.5 Hz, 1H), 3.63 (dd, J=10.5, 8.0 Hz, 1H), 3.23–3.20 (m, 1H), 3.12–3.07 (m, 1H), 2.88 (dd, J=19.0, 3.0 Hz, 1H), 2.47 (ddd, J=19.0, 4.5, 3.0 Hz, 1H), 2.17–2.11 (m, 1H), 2.08–2.02 (m, 1H), 1.86–1.80 (m, 1H), 1.78–1.71 (m, 1H), 1.50 (d, J=10.0 Hz, 1H), 1.50–1.43 (comp, 2H), 1.13 (s, 3H), 0.99 (s, 3H), 0.95 (d, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz) δ 172.2, 161.7, 121.0, 70.8, 48.4, 45.5, 44.9, 41.0, 37.3, 32.9, 32.7, 29.1, 28.2, 27.4, 17.8.

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