

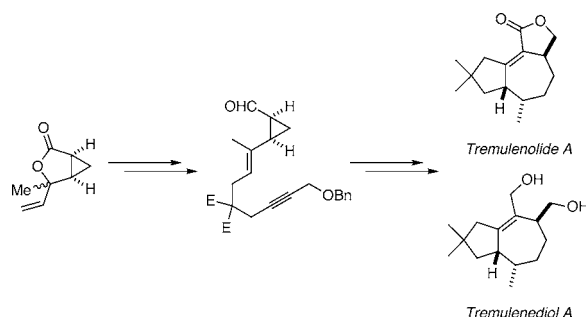
Enantioselective Syntheses of
Tremulenediol A and Tremulenolide A

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ABSTRACT

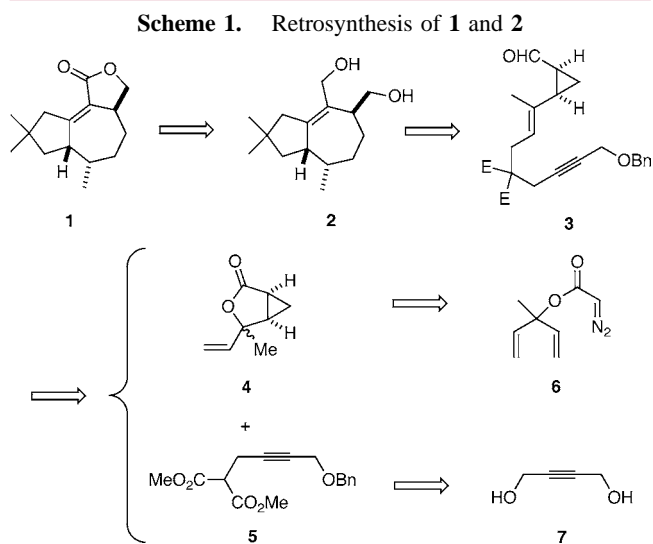


An enantioselective entry to the skeleton of the tremulane sesquiterpenes is described. The approach features a series of efficient transition metal-catalyzed reactions commencing with an enantioselective rhodium(II)-catalyzed intramolecular cyclopropanation followed by a regioselective allylic alkylation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

Tremulenolide A (**1**) and tremulenediol A (**2**), two representative members of the novel tremulane class of sesquiterpenes, were isolated in 1993 from the fungal pathogen *Phellinus tremulae* as part of a project to develop methods for controlling fungal decay and staining in trembling or quaking aspen (*Populus tremuloides*).¹ Although the commercial advantages associated with the potential biological activity that these two natural products may possess is intriguing in itself, the orientation and stereochemistry of the substituents on the hydroazulene skeleton was the primary motivation for our interest in **1** and **2** as synthetic targets. Although Davies reported a nice approach to racemic **1** and **2** in 1998,² there has been no report of an enantioselective synthesis of these interesting targets. We now report the enantioselective syntheses of **1** and **2** exploiting several transition metal-catalyzed reactions that have been of interest to us and others for a number of years.

The key features of our approach to tremulenolide A (**1**), which would be produced upon selective allylic oxidation of tremulenediol A (**2**), are outlined in retrosynthetic format in Scheme 1. The diastereoselective, Rh(I)-catalyzed [5 + 2] cycloaddition of the cyclopropyl 1,6-enyne **3** leading to

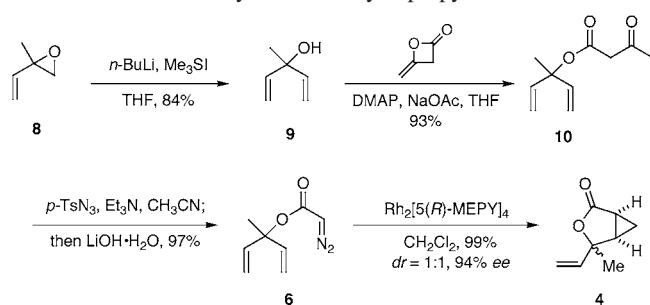
2 was inspired by the pioneering work of Wender.³ We envisioned that **3** would be accessible via a transition metal-catalyzed allylic alkylation of the vinyl cyclopropyl lactone



4 with the substituted malonate **5** prepared from 2-butyne-1,4-diol (**7**). The lactone **4** would then be prepared by the enantioselective, intramolecular rhodium(II)-catalyzed cyclopropanation of diazoester **6**, a reaction developed by our group over the past decade.⁴ We were optimistic that this synthetic strategy could be amended to incorporate the domino [Rh(CO)₂Cl]₂-catalyzed allylic alkylation/[5 + 2] cycloaddition reaction sequence that we recently reported,⁵ thus enabling a very rapid entry to the tremulane carbon skeleton.

The first phase of the synthesis entailed the enantioselective construction of cyclopropyl lactone **4** in a straightforward four-step sequence from commercially available 2-methyl-2-vinyl oxirane **8** (Scheme 2). Thus, treating oxirane **8** with

Scheme 2. Synthesis of Cyclopropyl Lactone **4**



the sulfur ylide generated from trimethylsulfonium iodide provided divinyl carbinol **9** in 84% yield.⁶ Because the tertiary alcohol group in **9** was resistant to acylation, it was not possible to prepare the diazoester **6** directly from **9** using the Corey–Myers diazoesterification procedure,⁷ and therefore, it became necessary to resort to an alternate protocol we had previously developed. In the event, acylation of **9** with diketene in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP) gave the β -ketoester **10** in 93% yield.⁸ Subsequent conversion of **10** to the corresponding 1,3-dicarbonyl diazo compound followed by hydroxide-induced cleavage of the methyl ketone moiety provided diazoester **6** in 97% overall yield. Cyclization of **6** via intramolecular cyclopropanation in the presence of Rh₂[5(R)-MEPY]₄ (0.1 mol %) proceeded smoothly to yield the cyclopropyl lactone **4** as a mixture (1:1) of C4 epimers

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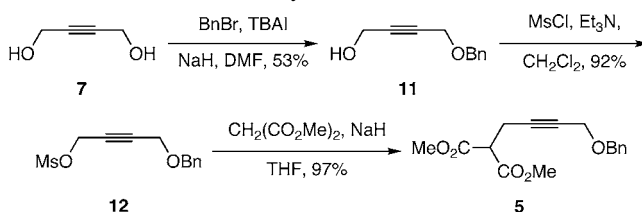
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(8) All new compounds were purified (>95%) by distillation, recrystallization, or preparative HPLC and were characterized by ¹H and ¹³C NMR, IR, and HRMS. Complete experimental details and characterization of new compounds will be published in a full account of this work.

in 99% combined yield and 94% ee for each diastereomer as determined by chiral HPLC analysis.

The synthesis of malonate **5** began with the monobenzylation of commercially available 2-butyne-1,4-diol (**7**) to give **11** (Scheme 3). In accord with literature reports,⁹ we found

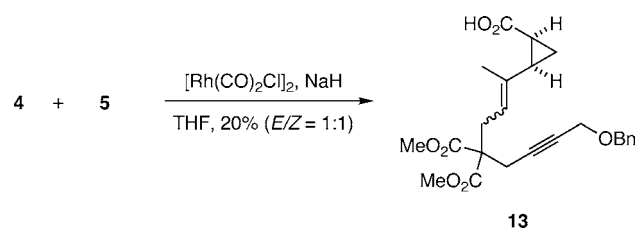
Scheme 3. Synthesis of Malonate **5**



that **7** could be converted into **11** in 51% yield upon treatment with benzyl bromide and Ag₂O. However, given the modest yield and cost of a silver-mediated reaction, we developed the less expensive alternative of reacting **7** with benzyl bromide, NaH, and tetrabutylammonium iodide (TBAI) in DMF to give **11** in 53% yield. Subsequent mesylation of **11** gave **12** (92%), which was then allowed to react with sodiodimethyl malonate to furnish **5** in 97% yield. Using this optimized three-step sequence, multigram quantities of **5** were readily obtained.

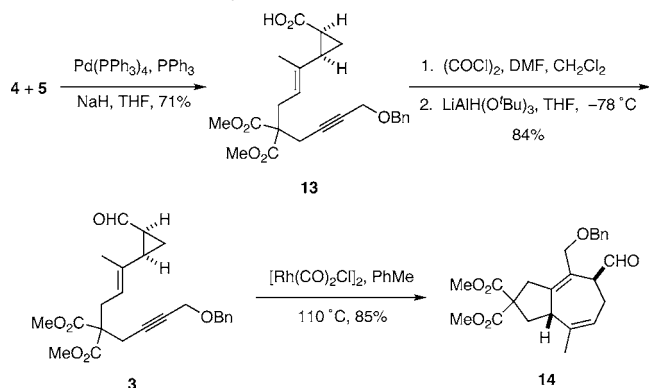
At this juncture, the stage was set for the preparation of **13** via a transition metal-catalyzed allylic alkylation of the vinyl cyclopropyl lactone **4** with a salt of malonate **5**. Inasmuch as [Rh(CO)₂Cl]₂ was known to catalyze the projected [5 + 2] cycloaddition that would form the hydroazulene ring, we queried whether it might also catalyze the desired allylic alkylation, thus potentially enabling a tandem allylic alkylation and [5 + 2] cycloaddition. We were of course cognizant of the work of Evans,¹⁰ who had shown that a modified Wilkinson's catalyst promoted allylic alkylations to give preferentially products in which substitution occurred at the more encumbered terminus of the allylic moiety. Not dissuaded by this unfavorable literature precedent, we discovered that when **4** was treated with the sodium enolate of **5** in the presence of [Rh(CO)₂Cl]₂, **13** was obtained with complete regiocontrol as a mixture (1:1) of *E/Z* isomers (Scheme 4), albeit in only a 20% yield that defied our attempts at optimization. It may be noted that this result led us to developing [Rh(CO)₂Cl]₂ as a novel catalyst having unique properties for allylic alkylations.¹¹

Scheme 4. Rh(I)-Catalyzed Allylic Alkylation of Cyclopropyl Lactone **4** with Malonate **5**



Given the poor efficiency with which $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ catalyzed the allylic alkylation of **4** with **5**, we turned to the use of more conventional Pd(0) catalysts and found that the reaction of **4** with the sodium enolate of **5** in the presence of 10 mol % of $\text{Pd}(\text{PPh}_3)_4$, and additional PPh_3 gave enyne **13** in 71% yield (Scheme 5). Although we were unable to

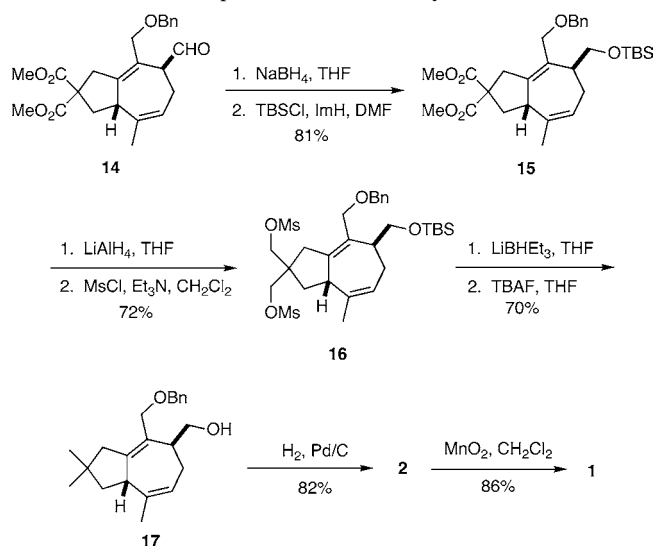
Scheme 5. Entry into the Tremulane Carbon Skeleton



effect the [5 + 2] cycloaddition of the carboxylic acid **13** to give the requisite hydroazulene, the $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ -catalyzed [5 + 2] cycloaddition of **3**, which was prepared in two steps and 84% overall yield from **13**, underwent facile intramolecular [5 + 2] cycloaddition upon heating in the presence of $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ to give **14** as the sole isolated product. The regiochemistry in this cycloaddition was consistent with the precedent of Wender.¹²

At this stage, our efforts focused on the task of reducing the diester moiety in **14** to install the requisite *gem*-dimethyl substitution present in tremulanes **1** and **2**. Toward this end, hydride reduction of **14** followed by protection of the resultant alcohol gave **15** in 81% overall yield (Scheme 6). Treatment of **15** with LiAlH_4 followed by mesylation of the resultant diol gave the corresponding bismesylate **16** in 72% overall yield. Initial attempts to reduce the bismesylate functionality to provide the *gem*-dimethyl moiety utilizing LiAlH_4 did not proceed to completion, even after extended reaction times (>24 h). However, reaction of **16** with LiBHET_3 followed by removal of the TBS protecting group delivered **17** in 70% yield over the two steps. When **17** was reduced via catalytic hydrogenation using base-washed Pd/C (10 mol %) under an atmosphere of H_2 , the trisubstituted olefin was reduced stereoselectively with concomitant removal of the benzyl protecting group to provide tremulenediol A (**2**) in 82% yield and as the only isolable product. The spectral data (e.g., 500 MHz ^1H and 125 MHz ^{13}C NMR and IR) for **2** were consistent with those reported in the literature,¹ and the optical rotation ($[\alpha]^{24}_\text{D} = +40.0$ (*c* 0.24

Scheme 6. Completion of the Total Syntheses of **2** and **1**



MeOH)) was comparable to that of natural **2** ($[\alpha]^{24}_\text{D} = +41.3$ (*c* 0.24 MeOH)). Subsequent treatment of **2** with MnO_2 provided lactone **1**, which exhibited spectral characteristics (e.g., 500 MHz ^1H and 125 MHz ^{13}C NMR) consistent with those reported in the literature. The optical rotation of synthetic **1** ($[\alpha]^{24}_\text{D} = +99.6$ (*c* 0.14 MeOH)) was comparable to that of the isolated natural product ($[\alpha]^{24}_\text{D} = +110.7$ (*c* 0.14 MeOH)).

In summary, the first enantioselective syntheses of the two representative *tremulane* sesquiterpenes tremulenolide A (**1**) and tremulenediol A (**2**) have been achieved. The synthetic route is highlighted by a chiral rhodium(II)-catalyzed enantioselective cyclopropanation to establish the requisite absolute stereochemistry of the natural products. A transition metal-catalyzed allylic alkylation is then utilized to assemble the complete carbon ensemble and to set up a diastereoselective rhodium(I)-catalyzed [5 + 2] intramolecular cycloaddition. Use of this trio of transition metal-catalyzed operations leads to the convergent and efficient total syntheses of **2** and **1** 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.

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Supporting Information Available: Experimental procedures for preparing **13** and **14** and copies of ^1H NMR spectra for all new compounds and synthetic **1** and **2**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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