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Approach to the Synthesis of Briarane Diterpenes through a Dianionic Claisen Rearrangement and Ring-Closing Metathesis

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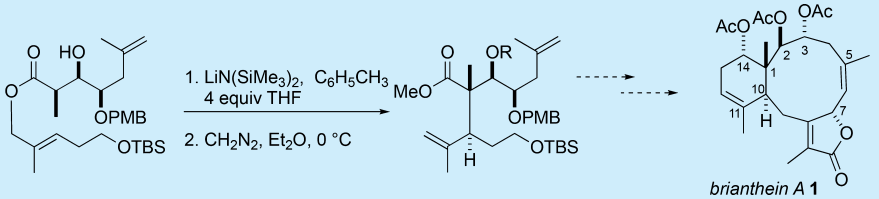
Supporting Information



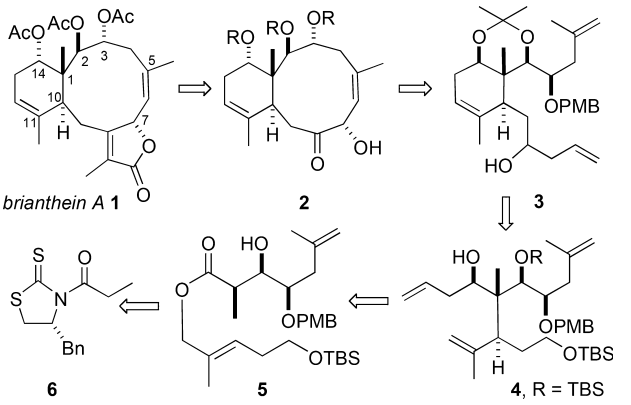
ABSTRACT: The synthesis of the briarane−brianthein A core has been accomplished utilizing an extension of the dianionic Ireland−Claisen rearrangement to establish the C1 quaternary carbon and the adjacent C10 ring juncture stereocenters. Two sequential ring-closing metathesis reactions were exploited to construct the 6−10 trans fused ring system.

The briarane diterpenes are a class of highly oxygenated marine metabolites that contain a modified cembranoid skeleton.[1] In the context of a broader program directed toward the synthesis of marine natural products,[2,3] we were attracted to the briaranes because of their unique structural features and intrigued by the relative lack of activity reported toward their synthesis.[4−9] Examination of the core carbocyclic structure of the briaranes reveals a trans-fused 6,10 carbon skeleton with an angular methyl group completing the substitution of a quaternary carbon at the ring fusion. The quaternary carbon center at the ring fusion and the 10-membered carbocyclic ring were of particular interest due to the paucity of general methods available for their construction.[10,11] Reported herein is an approach to the construction of the briarane skeleton focused toward the synthesis of brianthein A.

Of the multitude of briaranes that have been isolated and identified, brianthein A was chosen as an initial target because its carbocyclic skeleton possessed a relatively low level of oxygenation for a briarane but retained the interesting 6,10-fused carbocycle and the ring juncture quaternary stereocenter. The biological profile of brianthein was also of interest since it has been shown to reverse multidrug resistance (MDR) in human carcinoma cell lines, KB-C2, overexpressing P-glycoprotein.[12]

Our retrosynthetic plan for the synthesis of brianthein A (**1**) is illustrated in Scheme 1. Strategically, we anticipated appending the butenolide at a late stage to a core 6,10-carbocycle **2** that contained the remaining structural features of the molecule. The 6,10 bicycle **2** would be constructed by two sequential ring-closing metathesis (RCM) reactions. RCM of triene **4** would provide a cyclohexene which would be modified to triene **3**, the substrate for the RCM closure of the cyclodecene. The required ring fusion stereochemistry, including the quaternary carbon center, would be set by a

Scheme 1. Proposed Retrosynthesis of Brianthein A



dianionic Ireland−Claisen rearrangement of hydroxy ester **5**, which could be prepared through a diastereoselective thiazolidinethione mediated aldol addition.

We recently reported the development of the pivotal dianionic Ireland−Claisen rearrangement,[13] a modification of the classic Ireland−Claisen rearrangement of an allylic ester enolate that was initially disclosed by Kurth and co-workers.[14,15]

The Kurth method was extended to the construction of quaternary carbon centers by combining our thiazolidinethione mediated propionate aldol reaction[16] with the dianionic Ireland−Claisen rearrangement as shown in Scheme 2. The "Evans" *syn* propionate aldol adduct of *N*-propionylthiazolidinethione **6** proceeded in high yield and diastereoselectivity to give the aldol adducts **7**. Nucleophilic displacement of the chiral

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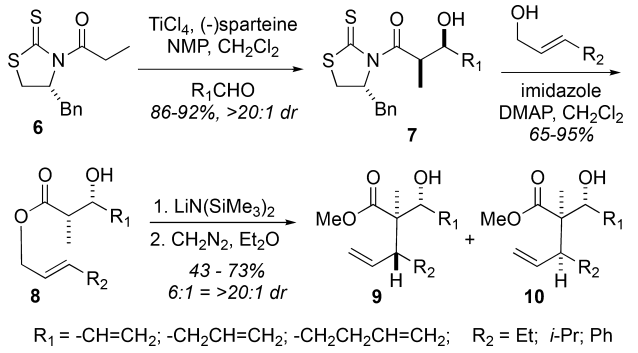
Scheme 2. Dianionic Ireland–Claisen Rearrangement

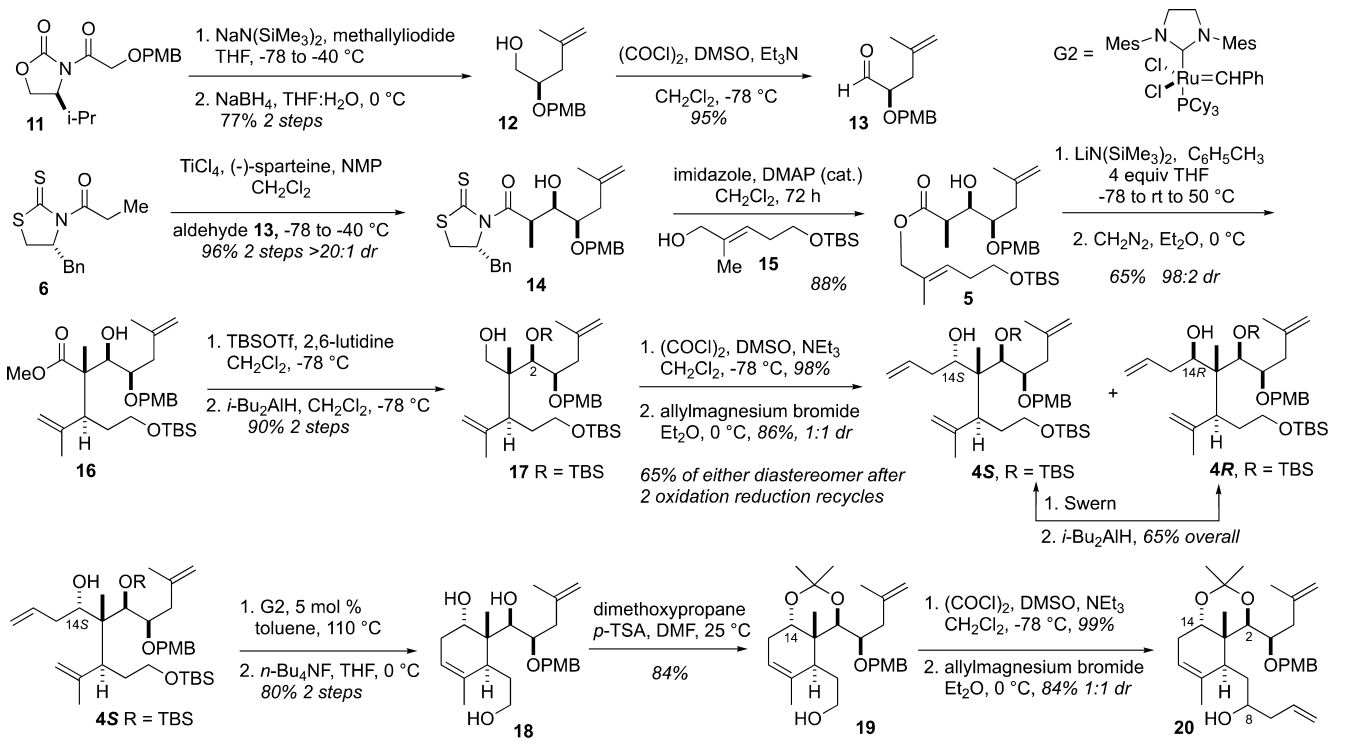


auxiliary under mild conditions with a variety of allylic alcohols produced the allylic esters **8** necessary for the dianionic Ireland–Claisen rearrangement study. The β-hydroxy allylic esters **8** were exposed to excess base $LiN(SiMe_3)_2$ in toluene with 4 equiv of THF and then warmed to room temperature. Excellent diastereoselectivity (ranging from 6:1 to >20:1) was observed.[13]

The application of the dianionic Claisen rearrangement to the construction of the carbocyclic core of brianthein A is presented here. The preparation of the hydroxyester **5** required for the strategic rearrangement is shown in Scheme 3. The requisite aldehyde **13**, needed for the initial aldol addition, was prepared from glycolyloxazolidinone **11**. Diastereoselective alkylation[17] of the sodium enolate of glycolate **11** followed by reductive removal of the auxiliary afforded primary alcohol **12** (77% overall). Alcohol **12** was oxidized to the aldehyde under Swern conditions,[18] and the aldehyde was used directly in an aldol addition with the chlorotitanium enolate of thiazolidinethione **6** to deliver the aldol adduct **14** (91% yield, > 20:1 dr; 2 steps). Exposure of aldol **14** to alcohol **15** in the presence of imidazole with catalytic DMAP afforded ester **5** in 88% yield, poised for the dianionic Ireland–Claisen rearrangement. The hydroxyester **5** was treated under the optimized conditions from the dianionic Ireland–Claisen studies and the resultant acid was esterified with diazomethane to provide ester **16** as the only detectable isomer (500 MHz NMR) in 72% yield. This reaction successfully established the two contiguous stereocenters that would constitute the ring juncture for the briarane core, including the quaternary carbon C1.

Transformation of ester **16** to the briarane core would require closure of the 6- and 10-membered rings[19] by sequential ring-closing metathesis reactions. The additional olefinic functionality needed to construct the 6-membered ring was incorporated as shown in Scheme 3. Protection of the C2-free alcohol **16** as the TBS ether and reduction of the ester afforded alcohol **17** in 90% yield. Swern oxidation[18] of alcohol **17** provided the aldehyde, which was treated with allylmagnesium bromide to afford a 1:1 mixture of diastereomers **4*S*/4*R*** in 84% yield. The *S* isomer could be recycled to the *R* diastereomer (or conversely the *R* isomer could be recycled to the *S* diastereomer) through an oxidation–reduction–recycle process since the isomeric alcohols were readily separable by chromatography. Attempts to set the C14 stereocenter in a more efficient manner with chiral allylating agents were unsuccessful. Further investigations focused on alcohol **4*S*** with the natural *S*-stereochemistry at C14. Exposure of **4*S*** to the Grubbs second-generation catalyst[20] in toluene at 110 °C provided the cyclohexene triol **18** in 80% yield for two steps after removal of the silyl ethers. Selective protection of the 1,3-diol as the acetonide afforded the primary alcohol **19** which was oxidized under Swern conditions.[18] The resultant aldehyde was treated with allylmagnesium bromide to produce an 86% yield of a mixture of C8 alcohols **20** poised for the ring closure to the 10-membered ring. When triene **20** was treated with

Scheme 3. Synthesis of the Cyclohexene Core of Brianthein A



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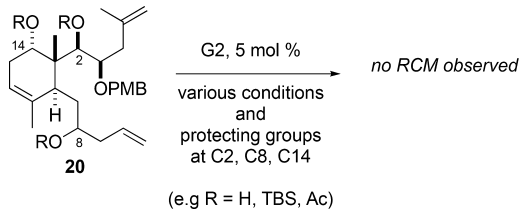
Grubbs second-generation catalyst in benzene at 80 °C no closure to the 10-membered ring was observed (Scheme 4).

Scheme 4. Attempted RCM of C14 *S* isomer



Additionally, various combinations of protecting groups at C2, C8, and C14 without cyclic constraints at C2−C14 (e.g., TBS, Ac, as well as free OH groups) were explored for the C14 *S* configuration **20**, but none of the desired RCM product could be detected with any of the protecting group combinations.

Analysis of the conformational preferences of the acetonides **20** and **3** (Figure 1) indicated that the conformations needed

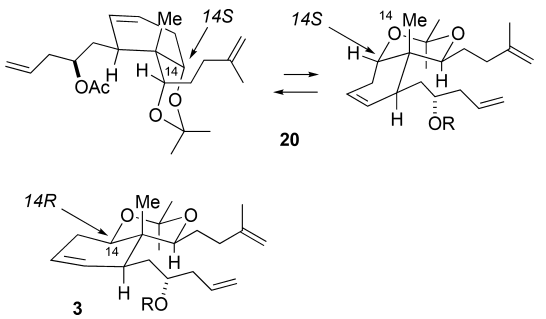


Figure 1. Conformations of acetonides **20** and **3**.

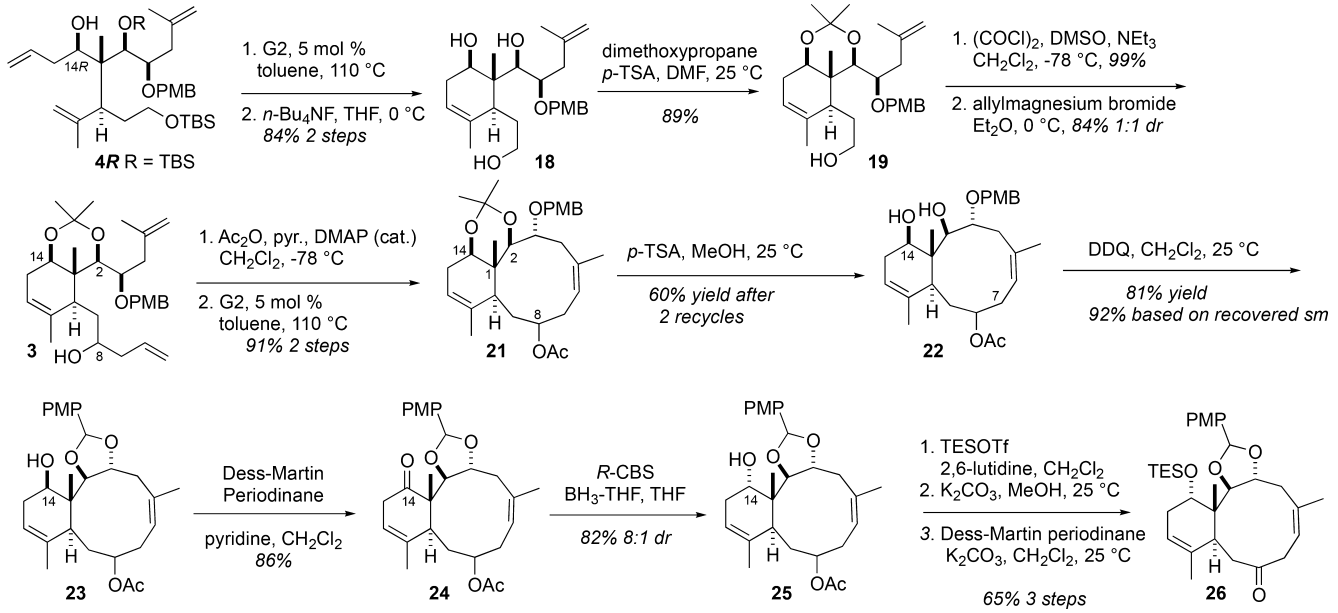
for the two alkene chains to undergo ring closure were not energetically favorable. In contrast, the unnatural *R* configuration of the C14 carbinol center provides a better opportunity to restrict the entropy of the pendant alkene chains and place them proximal for ring-closing metathesis to be successful. Consequently, preparation of the acetonide **3** was pursued to investigate its behavior in an RCM reaction to form the 10-membered ring.

The C14 *R* diastereomer **3** was prepared in an analogous fashion to acetonide **20** (Scheme 5). Triene **4*R*** readily formed the cyclohexene **18** upon treatment with the Grubbs G2 catalyst followed by global desilylation. Exposure of triol **18** to dimethoxypropane and *p*-TsOH selectively formed the C2−C14 acetonide **19** in 89% yield. The stereochemistry of **19**, and therefore, the stereochemistry at C2, C10, C14, and C15 was determined by X-ray analysis. Oxidation of the primary alcohol under Swern conditions[18] with subsequent addition of allylmagnesium bromide to the resultant aldehyde delivered a 1:1 mixture of alcohols **3** in 84% yield. The alcohols were separable and could be interconverted by oxidation reduction (1, Swern; 2, DiBAl-H), and only one diastereomer was carried forward for convenience of analysis. Upon conversion of the secondary alcohol to its corresponding acetate, it was gratifying to observe that exposure of the triene acetate to Grubbs G2 catalyst[20] in degassed toluene at reflux for 15 min produced the desired 6,10-fused bicyclic core structure **21** of brianthein A in >90% yield.

With the core structure of the briaranes constructed, it remained to invert the C14 stereocenter and append the butenolide to complete the synthesis of brianthein A. Beginning with the bicycle **21**, deprotection of the acetonide under acidic conditions resulted in partial cleavage of the acetate; however, a 60% yield of the hydroxyacetate **22** was achieved after two recycles (Scheme 5). Oxidation of the *p*-methoxybenzyl ether resulted in trapping by the neighboring free alcohol to afford the *p*-methoxyphenyl acetal **23** as a single diastereomer (92% brsm). Inversion of the free alcohol proceeded in an 8:1 dr via a Dess−Martin oxidation[21] to ketone **24** followed by a *R*-CBS reduction to give the C14 *S* diastereomer **25**.[22]

Our end-game strategy involved conversion of the C8 carbinol to a carbonyl as a handle to incorporate the butenolide. To that end, the C14 *S* diastereomer **25** was protected as the TES ether, whereupon deprotection of the acetate with potassium carbonate and methanol followed by Dess−Martin

Scheme 5. Completion of the Brianthein A Skeleton



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oxidation smoothly delivered ketone **26** in 86% yield (two steps). While selective deprotonation at the C7 position (supported by deuterium quenching studies) with LHMDS followed by oxidation of the enolate with the chiral camphorsulfonyl oxaziridine[23] afforded an α-hydroxyketone in good yield, further elaboration to brianthein A through standard butenolide synthesis strategies have been unsuccessful to date.[24]

In conclusion, we have demonstrated the utility of the dianionic Ireland–Claisen rearrangement in the construction of quaternary carbon stereocenters and applied this method to the synthesis of the brianthein A core. Additionally, the synthesis of the 10-membered ring via ring-closing metathesis was achieved through the use of strategically engineered conformational restraints.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01806.

Experimental procedures and full characterization data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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