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COMMUNICATION

Convergent Synthesis of the [5-7-6-3] Tetracyclic Core of Premyrsinane Diterpenes

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The [5-7-6-3] tetracyclic core of premyrsinane diterpenes was convergently synthesized via the stereoselective three-component coupling of a 2-propenyl unit, an enone, and an aldehyde, followed by the relay ring-closing metathesis with conformation control of the substrate to construct the 7-membered ring.

Premyrsinane diterpenes, which are the main ingredients extracted from the Euphorbiaceae family of flowering plants, have a [5-7-6-3] tetracyclic ring system (Figure 1a).[1] Biogenetically, starting from geranylgeranyl pyrophosphate (GGPP), the bicyclic casbane skeleton is first constructed, in which a *gem*-dimethylcyclopropane is fused to a cyclotetradecane ring. The cyclotetradecane ring is then divided into a cyclopentane ring and a cycloundecane ring via a transannular reaction, leading to the lathyrane skeleton (Figure 1b). The cycloundecane ring is further divided in several manners into a cyclohexane ring and a cycloheptane ring, resulting in the formation of [5-6-7-3] and [5-7-6-3] tetracyclic skeletons. Premyrsinane diterpenes belong to one of these diverse ring systems. Some premyrsinane diterpenes have an additional oxygen-containing ring as a cyclic ether or acetal.

Highly oxidized diterpenes are attractive synthesis targets because, in addition to construction of the skeletons, they often present synthetic challenges of introducing oxygen functionalities and controlling their reactivity.[2] For premyrsinane diterpenes, however, only a few synthetic studies have been reported. Yamamura's group reported a synthesis of the core structure of premyrsinane diterpenes via transannular reaction of an intermediate having the lathyrane skeleton.[3] Gao's group reported the conversion of the lathyrane skeleton into a premyrsinane skeleton via iron-catalyzed reductive olefin coupling.[4] Herein, we report the results of our study on the synthesis of premyrsinane diterpenes.

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Our retrosynthetic analysis is shown in Scheme 1. Oxygen functionalities at C13 and C14 would be introduced on a C-C double bond in **I**, which could be formed via a ring-closing metathesis (RCM).[5] The hydroxymethyl group at C6 would be introduced by a reaction at the α-position of the carbonyl group at C7. The requisite substrate **II** would, in turn, be prepared by a three-component coupling reaction of aldehyde **III**, enone **IV**, and 2-propenyl unit **V** via a sequence involving 1,4-addition and aldol reaction.[6]

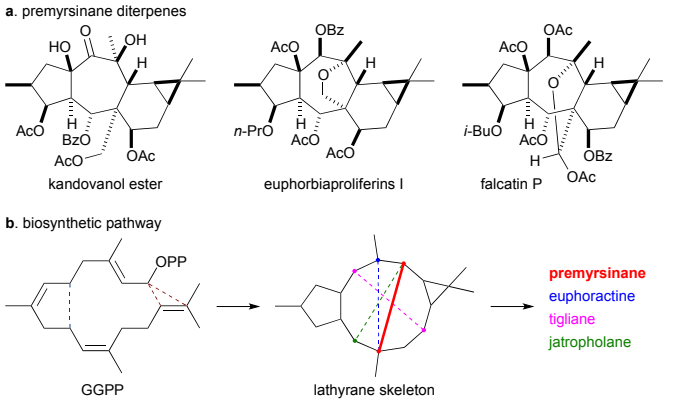
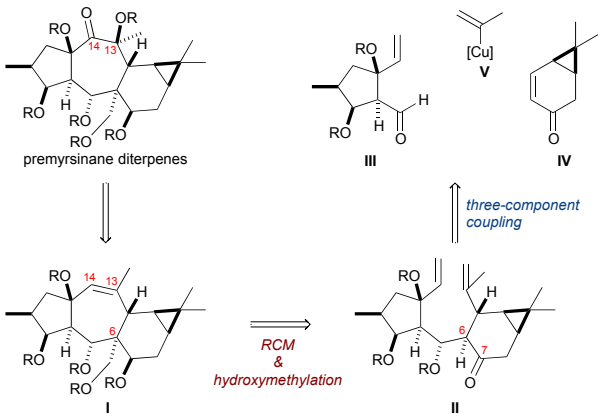
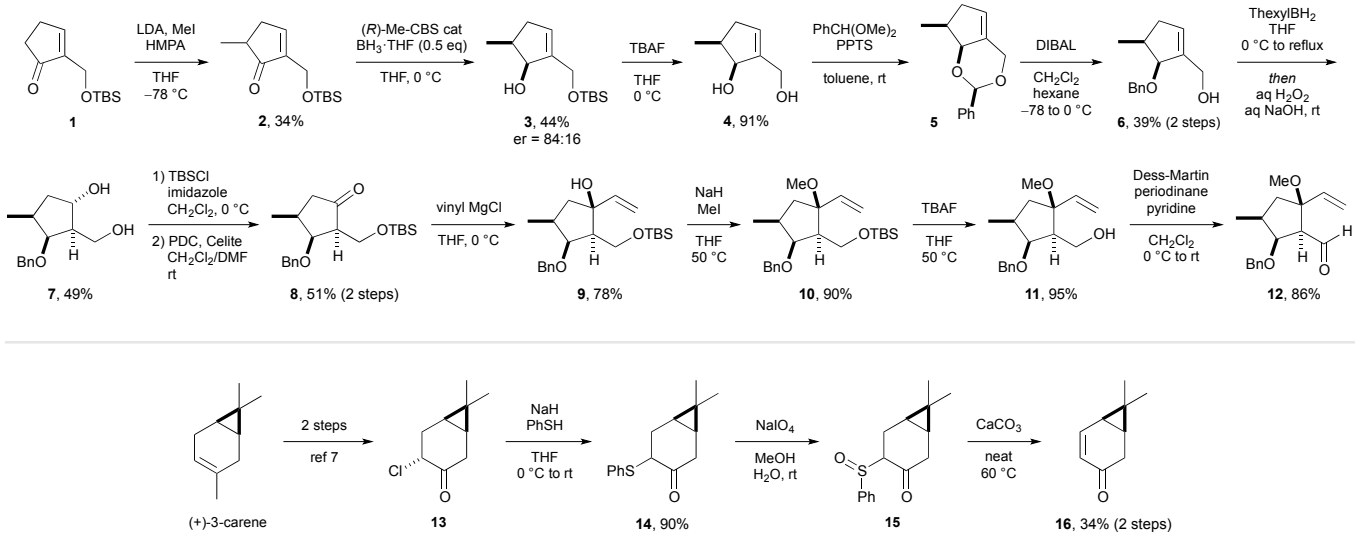


Figure 1. Premyrsinane diterpenes.



Scheme 1. Retrosynthetic analysis.

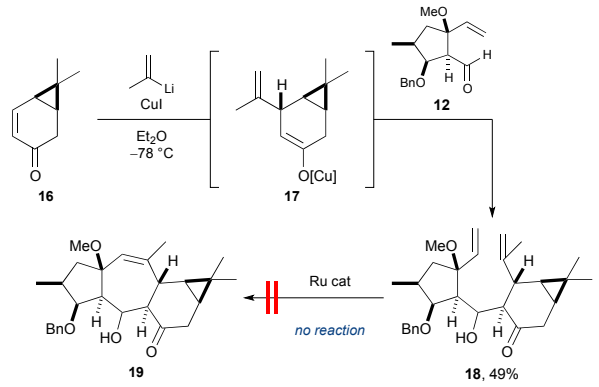


Scheme 2. Preparation of the aldehyde and enone units.

Our synthesis commenced with the preparation of aldehyde **12** (Scheme 2). Methylation of known cyclopentenone **1** gave **2**, which was subjected to Corey-Bakshi-Shibata (CBS) reduction.[7] Optical resolution occurred with moderate selectivity, and the resultant allylic alcohol **3** was obtained in 44% yield with an enantiomer ratio of 84:16. The absolute configuration of the major enantiomer was determined by the modified Mosher's method.[8] After removal of the *tert*-butyl(dimethyl)silyl (TBS) group, the resultant 1,3-diol **4** was converted into benzylidene acetal **5**, which was reductively cleaved with diisobutylaluminum hydride (DIBAL) to form benzyl ether **6**. Hydroboration with thexylborane proceeded stereoselectively to give diol **7**, which, after protection of the primary alcohol with a TBS group, was converted into ketone **8**. Treatment with vinyl magnesium chloride, followed by methylation of the resultant tertiary alcohol, afforded ether **10**. Removal of the TBS group and subsequent oxidation with Dess-Martin periodinane in the presence of pyridine furnished aldehyde **12**.

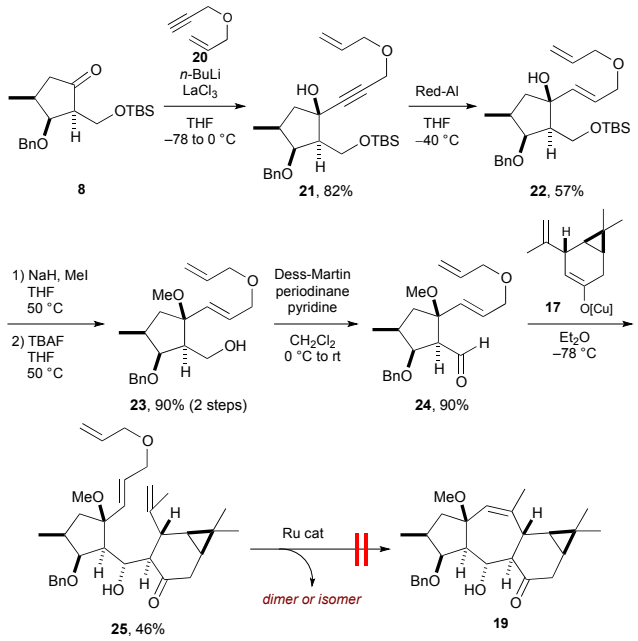
We next prepared enone **16** starting from (+)-3-carene. According to the reported procedure,[9] (+)-3-carene was converted into chloride **13** in two steps. Nucleophilic substitution with a thiolate smoothly proceeded, and the resultant sulfide **14** was oxidized with sodium periodate to give sulfoxide **15** as a mixture of diastereomers, which included a small amount of enone **16**. When the mixture was heated at 60 °C in the presence of $CaCO_3$, *syn*-elimination of the sulfoxide smoothly occurred to afford enone **16**.

With the desired aldehyde **12** and enone **16** in hand, we turned our attention to the three-component coupling reaction (Scheme 3). The 1,4-addition of a 2-propenyl copper reagent to enone **16** proceeded at –78 °C to generate enolate **17**, and addition of aldehyde **12** induced an aldol reaction to produce diene **18** as a single diastereomer.[10] The metathesis reaction, however, did not occur and diene **18** was recovered under conditions involving various Ru-based catalysts.[11] These results are attributed to the steric hindrance around the vinyl or 2-propenyl groups.



Scheme 3. Three-component coupling.

To make it easier to approach the double bonds, we decided to employ the relay ring-closing metathesis reaction (Scheme 4).[12] For the relay metathesis, we prepared the requisite substrate from ketone **8**. Nucleophilic addition of enyne **20**,[13] followed by reduction of the resultant propargyl alcohol **21** with Red-Al, afforded *E*-olefin **22**. Three-step conversions including methylation, desilylation, and oxidation gave aldehyde **24**. The three-component coupling reaction using aldehyde **24** also proceeded smoothly to give triene **25** in 46% yield as a sole isomer.[14] Attempted relay ring-closing metathesis reactions of triene **25**, however, did not produce the desired product **19**. Instead of the relay metathesis, cross metathesis between the terminal C-C double bond to form dimers, or isomerization of the terminal C-C double bond,[15] was observed.



Scheme 4. Attempted relay ring-closing metathesis.

Hoping to change the conformation and the reactivity, we converted the β-hydroxyketone moiety in **25** into a cyclic acetal (Scheme 5). Reduction with sodium borohydride ($NaBH_4$) occurred from the less-hindered face to furnish a 1,3-diol, which was reacted with benzaldehyde dimethyl acetal in the presence of pyridinium *p*-toluenesulfonate (PPTS) to afford benzylidene acetal **26**.[16] Upon treatment of **26** with Ru-based catalyst **27**[17] in refluxing toluene in the presence of 1,4-benzoquinone,[15] to our delight, the relay ring-closing metathesis reaction occurred to give a product with the [5-7-6-3] core (compound **28**) in 42% yield. Under these conditions, however, diene **29** was also produced in 26% yield via the relay cross metathesis, instead of the relay ring-closing metathesis.[18,19] NOESY correlations and coupling constants (*J* values) in ^{1}H-NMR of **26** showed that the cyclopentane moiety, which includes the diene unit, takes the axial position in the six-membered ring of the benzylidene acetal. In this conformation, the alkene moieties are apart from each other; therefore, the ring-closing metathesis requires a conformational change of the six-membered ring so that the cyclopentane moiety is situated in the equatorial position. If the stereoselectivity in the reduction of ketone **25** could be inverted, the cyclopentane moiety would take the equatorial position in the six-membered ring of the resultant benzylidene acetal. With these considerations in mind, we attempted reduction of the ketone directed by the β-hydroxy group with tetramethylammonium triacetoxyborohydride in a mixture of acetic acid and acetonitrile.[20] The reaction occurred stereoselectively to furnish the desired diol **30**, which was converted into benzylidene acetal **31**. The relay ring-closing metathesis reaction of **31** by treatment with catalyst **27** in refluxing toluene proceeded smoothly to give product **32** in 93% yield.

In conclusion, we achieved the synthesis of the [5-7-6-3] tetracyclic core of premyrsinane diterpenes. The three-component coupling of 2-propenyl cuprate, an enone and an aldehyde stereoselectively connected the cyclopentane unit and the cyclohexane unit fused to a cyclopropane ring. The relay ring-closing metathesis to construct the cycloheptane ring proceeded with control of the conformation of the substrate. These results will be helpful for constructing the skeleton of premyrsinane diterpenes and their related molecules.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

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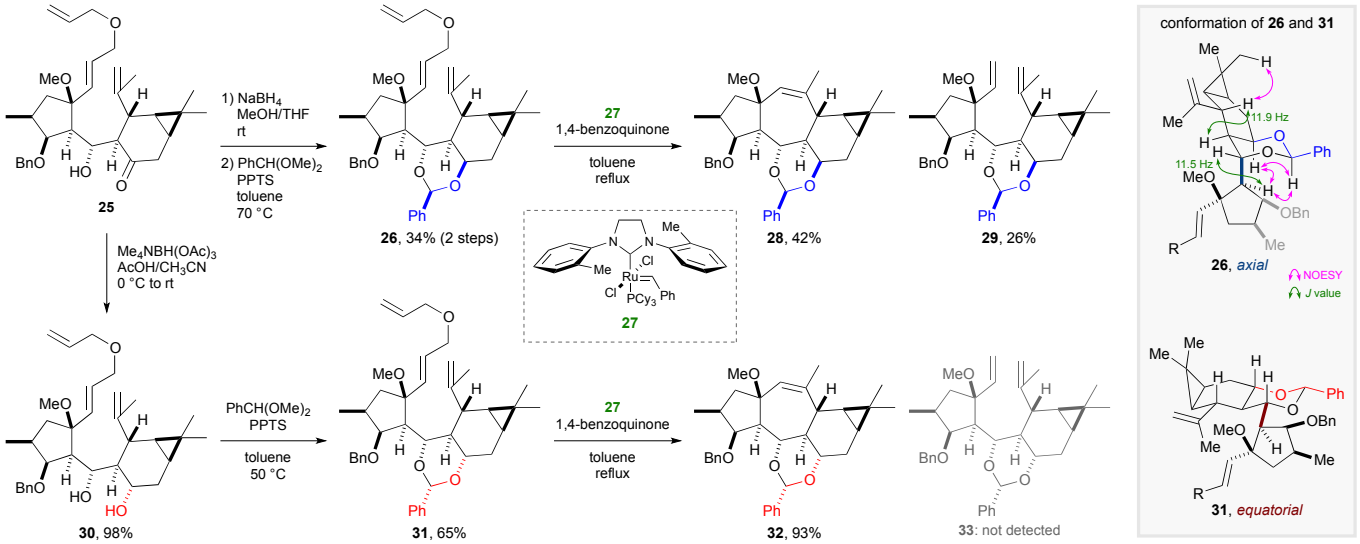

Scheme 5. Construction of the [5-7-6-3] tetracyclic skeleton via the relay ring-closing metathesis.

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10 Although the stereochemistry of **18** could not be determined at this stage, it was assumed to be the same as that of **25**.

11 The catalysts we used are listed in the Supporting Information (Figure S1).

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14 The stereochemistry of **25** was determined after conversion into **31** and **32**.

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16 The low yield of compound **26** is due to the reduction of **25** with $NaBH_4$ to produce a mixture of several compounds, which did not contain compound **30**.

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19 Exposure of **29** to the same conditions as the conversion of **26** into **28** resulted in no reaction. This strongly suggested that the vinyl and 2-propenyl group in **29** were inaccessible and that the relay metathesis was inevitable.

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