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## Synthesis of a biofuel target through conventional organic chemistry

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## ABSTRACT

In this work, the biofuel target compound 2-ethyl-5,5-dimethylcyclopenta-1,3-diene (**1**) and its exo isomers (**9a** and **9b**), were successfully synthesized via two different pathways from the common intermediate 4,4-dimethylcyclopent-2-ene-1-one (**2**). The first pathway produced the endocyclic product as a pure isomer via a triflate intermediate obtained from ketone **2** in 60% yield, followed by copper-catalyzed coupling with ethyl magnesium bromide in 63% yield. The second pathway employed a Grignard reaction with ketone **2**, which generated an alcohol that was immediately subjected to mild acid-catalyzed elimination to yield primarily a mixture of exo isomers **9a** and **9b** in 46% yield. The preparation method developed by this work allowed for the production of a sufficient quantity of these targets to evaluate their fuel properties, which will be reported in a separate study.

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## Introduction

The need for renewable sources of light, combustible hydrocarbons with low net-carbon footprints is growing in order to offset adverse effects such as climate change. The United States Department of Energy and similar institutions around the globe are currently searching for new transportation energy sources, with biomass-derived energy becoming widely employed to produce different fuel types from renewable feedstock.<sup>1</sup> The Co-Optimization of Fuels and Engines Initiative (Co-Optima) is a major collaboration of several national laboratories operated for the Department of Energy aimed at co-development of highly efficient engines and fuels. One of the goals of this work is to develop a method to produce multi-gram quantities of a potentially promising biomass-derived light hydrocarbon in order to test its fuel properties. Ultimately, it may be possible that the compound could be added to current commercial gasoline to allow spark ignition engines to run more efficiently should it be determined that the compound has promising fuel properties.

Several compounds were identified as potential fuel candidates by Strobel et al.,<sup>2</sup> in volatile hydrocarbons produced by the fungus *Gliocladium roseum*. The quantities produced were quite small, and were isolated for characterization purposes only. Subsequent efforts to synthesize the compounds in gram quantities by conventional methods were undertaken so that their fuel properties could be evaluated. The target compound 2-ethyl-5,5-dimethylcyclopenta-1,3-diene **1**, had been previously identified as part of a

major effort to find potential fuel candidates or blending components. To that end, several fuel properties such as boiling point, octane numbers, density, were calculated/simulated and this compound was determined to be one of interest.<sup>3</sup> The fuel properties evaluation is beyond the scope of this work, and will be disclosed in a future manuscript. This work describes the challenging synthetic pathways for **1**, one such target. The route to synthesize **1** would go through the known  $\alpha,\beta$ -unsaturated ketone **2** that had first been described by Magnus and coworkers (Scheme 1).<sup>4,5</sup> It was desired that the synthesis of compound **1** would occur via a suitable  $sp^2$  cross-coupling partner and subsequent attachment of the ethyl appendage. Furthermore, functionalized cyclopentadienes via cross-coupling are useful intermediate building blocks in natural product synthesis.<sup>6</sup>

## Results and discussion

The lack of advanced, reasonably priced commercial precursors required that a multistep synthesis be devised to prepare the target. One approach that was initially explored was the synthesis of the target from a pathway derived by Paquette et al.<sup>7</sup> to generate a key vinyl bromide intermediate that would undergo a final cross-coupling. However, this pathway involved a total of nine steps and delivered a 34% overall yield at best, while only producing a vinyl bromide that was at least one step away from the final compound. Attempts to reproduce the synthesis did not generate yields that approached those previously reported, and the intermediates required extensive purification. Therefore, an alternate pathway was investigated to make the key intermediate based on two *Organic Synthesis* preparations that followed the sequence outlined

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## Conclusion

For the two reaction pathways, the synthetic steps required to produce the target cyclopentadiene were significantly reduced when compared to making the vinyl bromide.<sup>6</sup> When the Grignard-elimination pathway is considered, in four steps, the overall yield was 43% of the two exo isomers, while the isomerically pure endo product was produced in five steps, with an overall yield of 21%. The reaction conditions were not optimized to improve yields. These modified pathways show promise for production of cyclopentadienes at scale, targeting a mixture of exo diastereomers or the pure endo isomer. Perhaps the most important contribution from this synthetic effort was the demonstration of a synthetic route to the cyclic 5,5-dimethyl-1,3-cyclopentadiene-2-triflic ester. There are no examples in the literature of this class of compounds, yet five-membered rings are a common structural motif in many organic targets. The expansion of stable 1,3-cyclopentadiene derivatives for cross-coupling and further manipulation would be of great benefit to synthetic chemists. This approach has demonstrated their preparation with relative ease and at a practical scale. One could envision a sequence of reactions starting from the triflate to rapidly add structural complexity through standard cross-coupling partners and cycloaddition strategies.

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## A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.tetlet.2018.02.073>. These data include MOL files and InChIKeys of the most important compounds described in this article.

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