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Reactivity study of isopiperitenol and *p*-mentha-2,8-dien-1-ol for the synthesis of cannabidiol and cannabidiolic acid methyl ester

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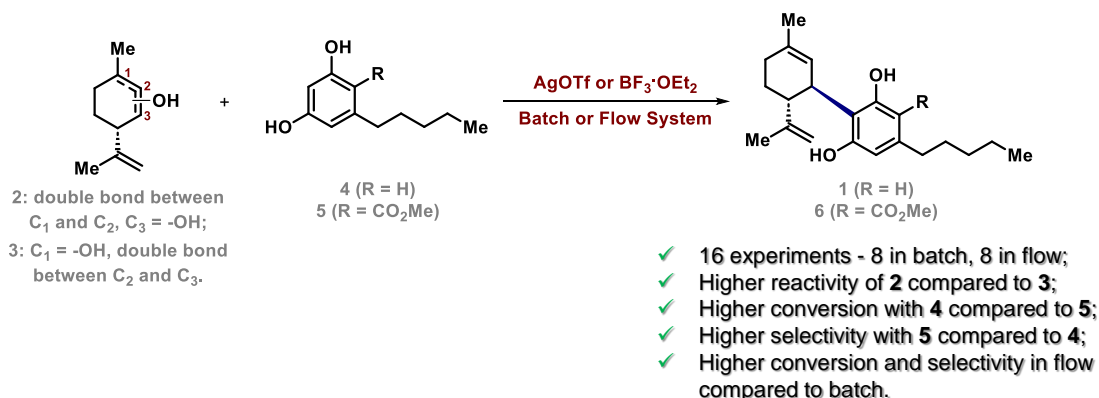
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ABSTRACT

Cannabidiol (**1**) is a phytocannabinoid with notorious pharmaceutical applications associated with its antiepileptic,¹ anxiolytic-like,² and chemoprotective properties.³ Hence, synthetic approaches targeting cannabidiol and other cannabinoids are encouraged. We highlight the Eschenmoser approach, which is based on a Friedel-Crafts reaction between an allylic alcohol, such as isopiperitenol (**2**) or *p*-mentha-2,8-dien-1-ol (**3**), and an olivetolic compound (**4** or **5**) in the presence of a Lewis acid.⁴ However, the difference in reactivity between alcohols **2** and **3** has never been investigated since the establishment of this strategy. Therefore, this study compares the reactivity of allylic alcohols **2** and **3** with compounds **4** and **5**, using AgOTf and BF₃·OEt₂ as Lewis acids, affording cannabidiol (**1**) or cannabidiolic acid methyl ester (**6**) in batch and flow systems. Reactions were monitored by HPLC-PDA. Our data showed that isopiperitenol (**2**) has higher reactivity than *p*-mentha-2,8-dien-1-ol (**3**). DFT calculations are being performed to complement the data obtained.



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