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Total synthesis of natural fregenedadiol and its diacetate, rearranged labdanes with aromatized B ring

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ABSTRACT

Labdane based natural products are most abundant and widely distributed in nature with many compounds exhibiting exceptional biological properties. Fregenedadiol is a bicyclic diterpene isolated from *Halimium viscosum* and represents a new carbon skeleton *fregenedane* with its B ring aromatized. Here, we report a total synthesis of this interesting natural product using one-pot Diels-Alder/aromatization sequence and selective hydrogenolysis as key steps.

The neutral part of *Halimium viscosum* (La Fregenda) is a repository of many natural products with bicyclic and tricyclic labdane skeletons.¹ These scaffolds have interesting biological and structural features. One such scaffold having rearranged labdane with aromatized B ring is 'fregenedane' and its corresponding natural products fregenedadiol (**1**) and fregenedadiol diacetate (**2**) were isolated by Urones and co-workers². Their structures have been determined using various spectroscopic methods and later confirmed by semi-synthesis.³ Very few bicyclic diterpenes are known in nature with this aromatized B ring⁴ (few of them listed in figure 1). Out of them, fregenedadiol (**1**) and its isomer isofregenedadiol (**3**) have an additional C3 hydroxyl substitution with *S* stereochemistry. The total synthesis of related molecules chrysolic acid (**4**) and isofregenedol (**5**) were reported in the literature.⁵ However, there has been only semi-synthetic approaches developed to access fregenedadiol.³ Even though biological activity of fregenedadiol is not reported, related labdanes are known to exhibit a wide range of biological properties⁶ such as anti-mutagenic, anti-bacterial, anti-fungal, cytotoxic, anti-inflammatory and analgesic etc. In addition, there are a few reports on medicinal properties of compounds with tetrahydronaphthalene core.⁷ Therefore, we became interested in this class of compounds and a few years

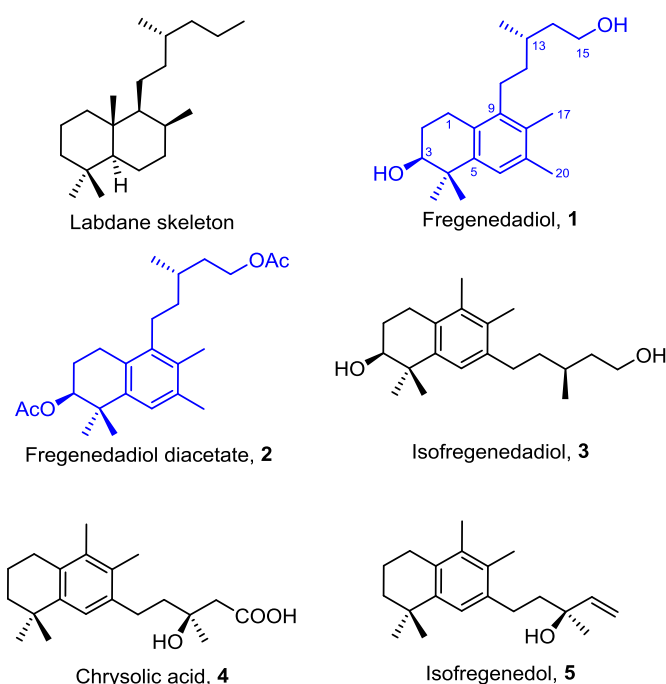


Figure 1. Structures of natural products containing aromatic B ring

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