Cannabidiol as the Substrate in Acid-Catalyzed Intramolecular Cyclization

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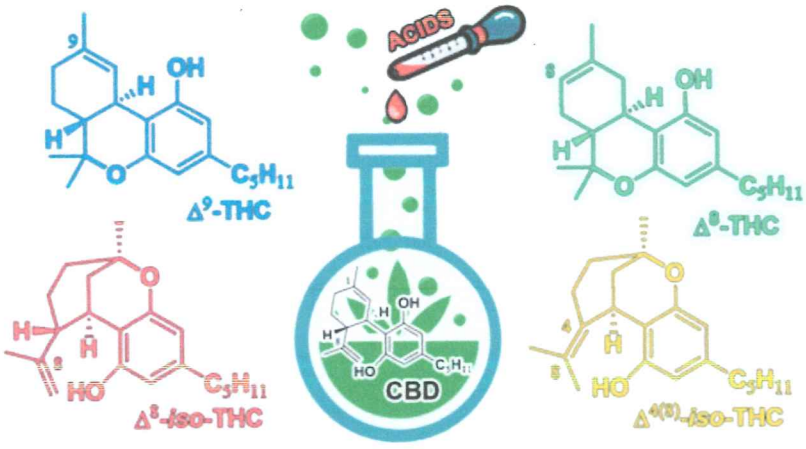
Abstract



The chemical reactivity of cannabidiol is based on its ability to undergo intramolecular cyclization driven by the addition of a phenolic group to one of its two double bonds. The main products of this cyclization are Δ^9-THC (*trans*-Δ-9-tetrahydrocannabinol) and Δ^8-THC (*trans*-Δ-8-tetrahydrocannabinol). These two cannabinoids are isomers, and the first one is a frequently investigated psychoactive compound and pharmaceutical agent. The isomers Δ^8-*iso*-THC (*trans*-Δ-8-*iso*-tetrahydrocannabinol) and $\Delta^{4(8)}$-*iso*-THC (*trans*-Δ-4,8-*iso*-tetrahydrocannabinol) have been identified as additional products of intramolecular cyclization. The use of Lewis and protic acids in different solvents has been studied to investigate the possible modulation of the reactivity of CBD (cannabidiol). The complete NMR spectroscopic characterizations of the four isomers are reported. High-performance liquid chromatography analysis and ^{1}H NMR spectra of the reaction mixture were used to assess the percentage ratio of the compounds formed.

Recent years have seen a dramatically increasing interest in phytocannabinoids. Isolated from *Cannabis* in 1940, (1,2) cannabidiol (CBD) is one of the most abundant phytocannabinoids in the species of *Cannabis* for textile uses. (3,4) Despite the structural similarity between CBD and Δ^9-THC (*trans*-Δ-9-tetrahydrocannabinol) (Figure 1), CBD has a low agonistic effect for cannabinoic receptors; in particular, it is considered an allosteric negative modulator of CB1 and CB2 receptc (cannabinoid receptor types 1 and 2). (5,6) Current evidence shows that CBD exerts