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Articles

# Studies Pertaining to the Emerging Cannabinoid Hexahydrocannabinol (HHC)

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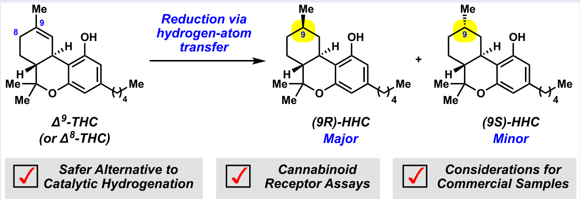
**ABSTRACT:** We report studies pertaining to two isomeric hexahydrocannabinols (HHCs), (9*R*)-HHC and (9*S*)-HHC, which are derivatives of the psychoactive cannabinoids $\Delta^9$- and $\Delta^8$-THC. HHCs have been known since the 1940s, but have become increasingly available to the public in the United States and are typically sold as a mixture of isomers. We show that (9*R*)-HHC and (9*S*)-HHC can be prepared using hydrogen-atom transfer reduction, with (9*R*)-HHC being accessed as the major diastereomer. In addition, we report the results of cannabinoid receptor studies for (9*R*)-HHC and (9*S*)-HHC. The binding affinity and activity of isomer (9*R*)-HHC are similar to that of $\Delta^9$-THC, whereas (9*S*)-HHC binds strongly in cannabinoid receptor studies but displays diminished activity in functional assays. This is notable, as our examination of the certificates of analysis for >60 commercially available HHC products show wide variability in HHC isomer ratios (from 0.2:1 to 2.4:1 of (9*R*)-HHC to (9*S*)-HHC). These studies suggest the need for greater research and systematic testing of new cannabinoids. Such efforts would help inform cannabis-based policies, ensure the safety of cannabinoids, and potentially lead to the discovery of new medicines.



## ■ INTRODUCTION

The cannabis industry has undergone remarkable evolution in recent years. Despite marijuana, cannabis having ≥0.3% (weight/weight) of $\Delta^9$-*trans*-tetrahydrocannabinol ($\Delta^9$-THC, see compound **1**, Figure 1),[1] being illegal in many parts of the world and stigmatized for decades, many states in the United States (U.S.) have now legalized or decriminalized the use of marijuana-based products.[2] Similarly, there has been an increase in U.S. Federal legislation,[2,3] with a particular focus on accelerating the pace of research needed to address numerous challenges in the field.[4−6]

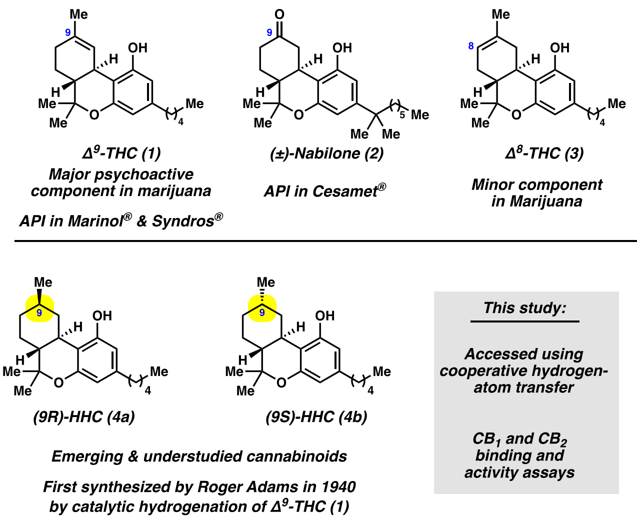


**Figure 1.** Cannabinoids **1**−**3** and emerging cannabinoids HHCs **4a** and **4b**.

One major contemporary challenge involves the availability of derivatives of $\Delta^9$-THC (**1**, Figure 1),[7] which is the primary active component of marijuana that is associated with intoxication. However, from a therapeutic standpoint, **1** is also the active pharmaceutical ingredient (API) in the FDA-approved drugs Marinol and Syndros. These drugs are used to treat nausea and vomiting caused by cancer chemotherapy, in addition to loss of appetite and weight loss in patients with HIV/AIDS. Whereas **1** on its own is a Schedule 1 substance, Marinol is a Schedule 3 substance, and Syndros is a Schedule 2 substance.

Not surprisingly, analogs of **1** have similarly become highly sought after for both medicinal and nonmedicinal purposes.[8] THC derivatives **2** and **3** provide illustrative examples. Nabilone (**2**) is sold as a racemate under the trade name Cesamet and is used for the treatment of chronic pain (in Canada). It is also FDA-approved for chemotherapy-induced vomiting or nausea (in the U.S.). A contrasting example is $\Delta^8$-*trans*-tetrahydrocannabinol ($\Delta^8$-THC, **3**), a minor constituent

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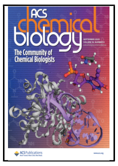


of cannabis with a structure similar to **1**. Δ$^8$-THC (**3**) has become commonly available to the public in many states, both with and without marijuana legalization, yet remains non-FDA-approved, unregulated, and generally understudied.[9]

The present study focuses on related cannabinoids called hexahydrocannabinols (HHCs).[10,11] Despite being relatively understudied since the first synthesis by Adams in 1940,[12] these compounds are now becoming increasingly widespread and can be purchased in some states in the U.S. Conflicting views regarding the federal legality of HHCs exist. One perspective is that HHCs are legal as a result of the U.S. 2018 Farm Bill. On the other hand, the U.S. Drug Enforcement Administration (DEA) has informed us that they consider HHCs of the type described herein Schedule 1 substances.

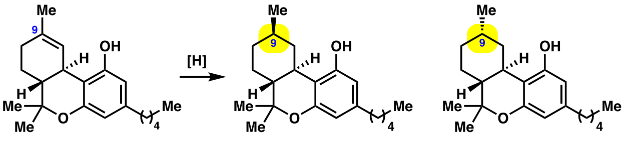
When HHCs are accessed synthetically from Δ$^9$-THC (**1**) or Δ$^8$-THC (**3**), two diastereomers can form: (*9R*)-HHC **4a** and (*9S*)-HHC **4b** (Figure 1). The *9R* isomer, **4a**, is sometimes referred to as the "methyl equatorial" isomer of HHC in the literature, whereas the *9S* isomer, **4b**, is sometimes referred to as the "methyl axial" isomer. These HHC diastereomers vary based on the stereochemistry at C9. It is expected that different properties and biological effects exist for the two diastereomers. The ratio of isomers **4a** and **4b** within commercially available HHC varies significantly, as will be discussed further in this Letter, presumably based on the method of production and purification. Most commonly, **4a** and **4b** are prepared using catalytic hydrogenation,[12−15] which yields a mixture of isomers with low selectivity. In addition, fires, runaway reactions, and explosions are well-known dangers associated with catalytic hydrogenation and such dangers can vary based on the conditions employed.[16−19] Lastly, trace heavy metals (e.g., Pt or Pd) may remain after catalytic hydrogenation due to leaching or dissolution. The extent to which trace metals remain can vary based on the catalyst employed, the reaction conditions used, as well as the exact purification methods.[20,21] The presence of residual heavy metals bears significant toxicity concerns.

Limited biological studies of HHCs **4a** and **4b** are available in the literature.[22−31] The psychoactive effects of **4a** and **4b** have been demonstrated in rabbits[24] and nonhuman primates,[22,23,25] using either individual isomers or mixtures. With regard to therapeutic potential, studies have shown that HHCs **4a** and **4b** may be valuable leads for the treatment of colon cancer[26] and ocular hypotony.[27] One recent study shows promising cardiac safety and cytotoxicity profiles for the mixture of HHC isomers using in vitro assays.[28] There is also one report regarding the in vitro binding affinity of (±)-**4a** in human cannabinoid receptors.[30] Systematic in vitro assay data showing potency or binding affinity of enantioenriched **4a** or **4b** to the cannabinoid receptors type 1 or 2 (CB$_1$ or CB$_2$), have yet to be published. Of note, cannabinoids that bind to either the CB$_1$ or CB$_2$ receptor may be associated with both adverse effects and therapeutic potential, depending on a variety of factors.[32,33] Cannabinoids that bind to the CB$_1$ receptor are also commonly associated with intoxicating effects. Individually investigating the biological characteristics of HHC isomers **4a** and **4b** would provide insight into their therapeutic potential.

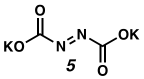
With the aforementioned considerations, we sought to (a) develop a means to synthesize both isomers of HHC that avoids the use of potentially dangerous catalytic hydrogenation conditions and toxic heavy metals and (b) establish their affinity and activity at human CB$_1$ and CB$_2$ receptors relative to Δ$^9$-THC (**1**). Here, we report the use of cooperative hydrogen-atom transfer (HAT) to convert Δ$^9$-THC (**1**) and Δ$^8$-THC (**3**) to HHCs **4a** and **4b**.[34] In contrast to results obtained by using catalytic hydrogenation, **4a** is formed as the major product using the HAT protocol. Additionally, we demonstrate via biological investigation that **4a** and **4b** possess significantly different binding affinities and potency, with **4a** exhibiting similar activity compared with Δ$^9$-THC (**1**). Finally, we examine the certificates of analyses for >60 commercially available HHC products, which show wide variability in HHC isomer ratios. These studies are expected to prompt further scientific investigation of HHCs, and also underscore the importance of performing such synthetic and biochemical studies as new cannabinoids inevitably emerge.

**Reduction of Δ$^9$-THC (1) and Δ$^8$-THC (3).** To initiate our studies, we investigated the reduction of Δ$^9$-THC (**1**) to afford HHCs **4a** and **4b** (see Table 1). We first attempted catalytic hydrogenation conditions, since literature data did not consistently report diastereoselectivities or yields. We began with the use of PtO$_2$, which Adams had demonstrated in the 1940s for the reduction of **1**.[12] This gave roughly equimolar

**Table 1. Reduction Studies of Δ$^9$-THC (1) To Furnish HHCs 4a and 4b**



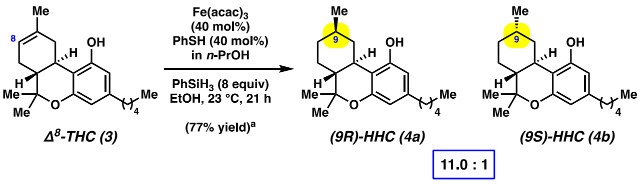
*Δ$^9$-THC (1)* *(9R)-HHC (4a)* *(9S)-HHC (4b)*

| *Entry* | *Conditions* | *Yield of 4a + 4b$^a$* | *Ratio 4a to 4b$^b$* |
|---|---|---|---|
| *1* | PtO$_2$ (10 mol%), H$_2$ (1 atm)<br>AcOH, 23 °C, 4 h | 79% | 1.1 : 1 |
| *2* | Pt/C (10 mol%), H$_2$ (1 atm)<br>EtOH, 23 °C, 16 h | 71% | 1 : 1.1 |
| *3* | Rh/C (10 mol%), H$_2$ (1 atm)<br>EtOH, 23 °C, 16 h | 0% | – |
| *4* | Pd/C (10 mol%), H$_2$ (1 atm)<br>EtOH, 23 °C, 24 h | 76% | 1 : 3.9 |
| *5* | [Ir(cod)PCy$_3$Pyr]$^+$PF$_6^-$ (10 mol%)<br>H$_2$ (1 atm), CH$_2$Cl$_2$<br>0 → 23 °C, 4 h | 63% | 1 : 2.0 |
| *6* | RhCl(PPh$_3$)$_3$ (10 mol%), H$_2$ (1 atm)<br>benzene:EtOH (1:1), 23 °C, 16 h | 0% | – |
| *7* |  *5*<br>(3 equiv)<br>AcOH (8 equiv)<br>EtOH, 23 °C, 16 h | trace | – |
| *8* | CoCl$_2$ (50 mol%)<br>LiAlH$_4$ (50 mol%), THF<br>–78 → 23 °C, 4 h | 11% | not determined |
| *9* | Fe(acac)$_3$ (10 mol%)<br>PhSH (10 mol%) in *n*-PrOH<br>PhSiH$_3$ (2 equiv)<br>EtOH, 23 °C, 27 h | 23%$^{c,d}$ | 9.4 : 1 |
| *10$^e$* | Fe(acac)$_3$ (40 mol%)<br>PhSH (40 mol%) in *n*-PrOH<br>PhSiH$_3$ (8 equiv)<br>EtOH, 23 °C, 21 h | 74%$^{c,f}$ | 9.5 : 1 |

[a] Isolated yields. [b] Ratios determined from isolated material using $^1$H NMR. [c] Yields reflect the average of two isolation experiments. [d] 38% yield of recovered **1**, average from two isolation experiments. [e] 20 mol % of Fe(acac)$_2$, 20 mol % of PhSH, and 4 equiv PhSiH$_3$ were initially added portionwise, followed by the second portion after 17 h. [f] 10% yield of recovered **1**, average from two isolation experiments.

amounts of **4a** and **4b** (entry 1 in Table 1). Similar results were seen when Pt/C was used (entry 2 in Table 1). Although the use of Rh/C proved to be ineffective (entry 3 in Table 1), hydrogenation using Pd/C delivered **4a** and **4b** in a ratio of 1 to 3.9, respectively (entry 4 in Table 1). We then examined homogeneous hydrogenation conditions that were not known for the reduction of **1** in the literature. The use of Ir catalyst (Crabtree's catalyst) proved less effective (entry 5 in Table 1), while Rh catalyst (Wilkinson's catalyst) was unsuccessful (entry 6 in Table 1). The reduction with diimide **5** also proved unproductive (entry 7 in Table 1). Stoichiometric metal hydride conditions gave low yields (entry 8 in Table 1).[35] Lastly, we evaluated HAT conditions, which are attractive due to the avoidance of pyrophoric reagents and high levels of thermodynamically controlled diastereoselectivity.[36] Such conditions had not been reported for the reduction of **1**. The Fe-based protocol reported by West was especially attractive,[37] as the necessary reagents are commercially available and iron is considered a metal of minimal concern.[20] Employment of the West conditions gave good diastereoselectivity (entry 9 in Table 1) but a low yield. By increasing the loading of reagents and adding them portionwise over two additions, the combined yield of **4a** and **4b** increased to 74%, with a **4a**:**4b** ratio of 9.5:1 (entry 10 in Table 1). It is notable that the HAT conditions provide the highest selectivity and favor the formation of isomer **4a**. In consideration of the results described in the subsequent section pertaining to biological assays, the observed preference for **4a** proved to be a fortuitous result. We also examined the HAT reduction of the $\Delta^9$-THC (**1**) isomer $\Delta^8$-THC (**3**). As shown in Scheme 1, treatment of **3** under our previously optimized conditions afforded HHCs **4a** and **4b** in 77% yield. Of note, the **4a**:**4b** ratio was 11.0 to 1, respectively, which reflects comparable selectivity to the diastereoselectivity observed when $\Delta^9$-THC (**1**) is employed. These results show that either THC isomer (i.e., **1** or **3**) can be used in the reduction.

**Scheme 1. HAT Reduction of $\Delta^8$-THC (3) To Give HHCs 4a and 4b**



[a] Yield reflects the average of two isolation experiments.

In order to rationalize the diastereoselectivity in the HAT reduction of **1** and **3**, we considered the relative energies of **4a** and **4b**. A 1989 study by Reggio and co-workers suggested that **4a** is energetically favorable,[38] but computations using higher levels of theory now accessible have not been performed. As such, we conducted density functional theory (DFT) calculations using ωB97X-D (6-31G*) for **4a-Me** and **4b-Me**, which are the simplified structures (i.e., methyl in place of pentyl) shown in Figure 2. Following conformational searching, the lowest ground-state energies were compared. Of note, **4a-Me** was found to be thermodynamically favored by 1.42 kcal/mol. This difference in energy corresponds to a diastereomeric ratio (dr) of ~10:1, which is consistent with our experimental observations. In accordance with general mechanistic considerations for HAT reductions,[36] thermodynamic control is presumably operative in the reductions of **1** or **3** to favor formation of the product bearing an equatorial methyl group (i.e., **4a**, analogous to computed structure **4a-Me**).

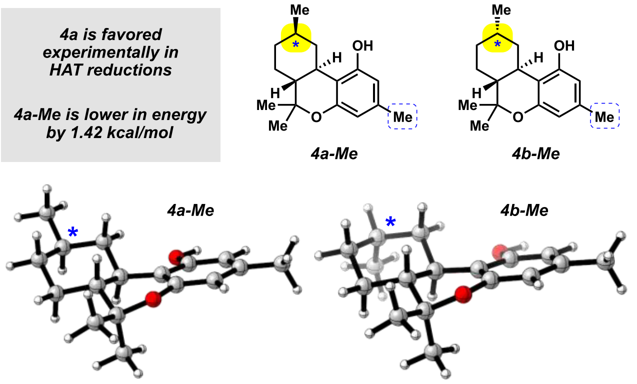
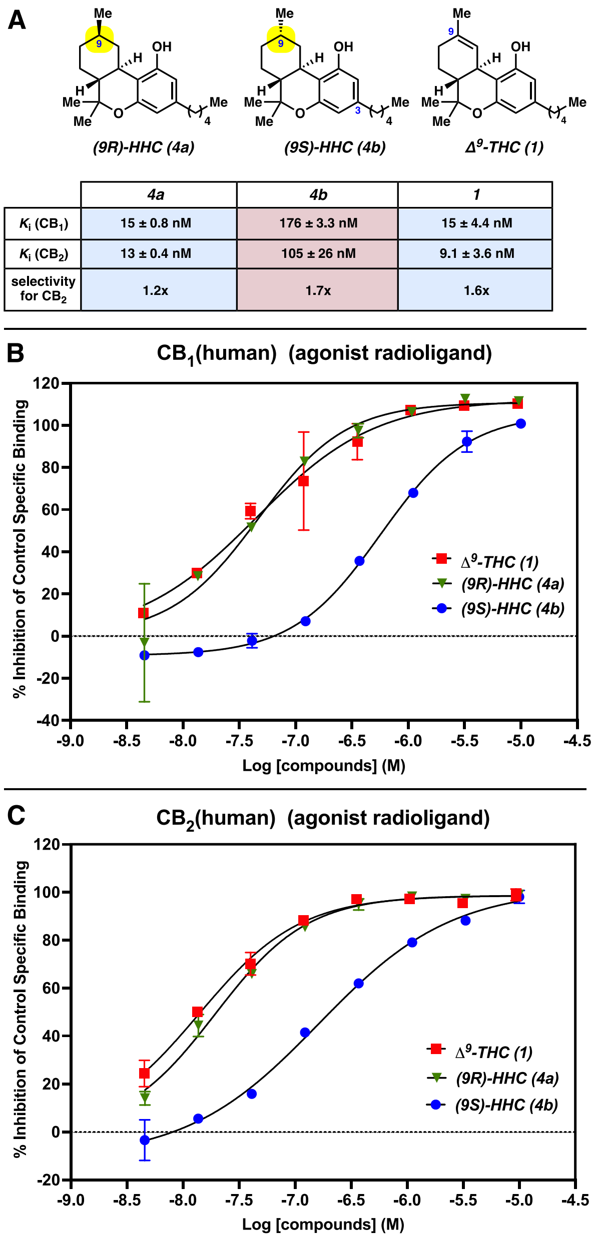


**Figure 2.** Lowest energy conformers for **4a-Me** and **4b-Me**. Structures are displayed by using CYLview.

**$CB_1$ and $CB_2$ Receptor Studies.** As discussed earlier, two receptors, $CB_1$ and $CB_2$, are important for assessing the biological activities of cannabinoids. Interactions with $CB_1$ or $CB_2$ can be useful for therapeutic purposes.[32,33] Given that the individual activities of **4a** and **4b** in human $CB_1$ and $CB_2$ receptor assays are not described in the literature, we sought to study this further. Pure synthetic samples of **4a** and **4b** were prepared (>19:1 dr) for use in cannabinoid receptor studies. Given the relative product distribution of the different reduction protocols, **4a** was accessed using HAT reduction of **1**, whereas **4b** was prepared using catalytic hydrogenation of **1** (see the SI for details). Biological assays were performed by Eurofins Discovery. A radioligand binding assay was used to determine $K_i$ and $IC_{50}$ values.[39,40] A G-protein coupled receptor (GPCR) functional assay was used to study potency and determine $EC_{50}$ values.[41] Both assays use human cannabinoid receptors with the appropriate reference standards (see the SI for details). $\Delta^9$-THC (**1**), a known partial agonist for both $CB_1$ and $CB_2$, was simultaneously evaluated to provide a point of comparison under the same assay conditions.[42]

The $CB_1$ binding assay was conducted with cellular lysates of Chem-1 cells transfected with human $CB_1$ cannabinoid receptor. Displacement of radio-labeled [$^3$H]CP 55940[43] by the tested compounds measured specific binding and WIN 55212-2[44] was used to determine nonspecific binding. The $CB_2$ binding assay was conducted with cellular lysates of CHO cells transfected with the human $CB_2$ cannabinoid receptor. Displacement of radio-labeled [$^3$H]WIN 55212-2 by the tested compounds measured specific binding and WIN 55212-2 was used to determine nonspecific binding. Both **4a** ($K_i$ = 15 nM at $CB_1$ and 13 nM at $CB_2$) and **4b** ($K_i$ = 176 nM at $CB_1$ and 105 nM at $CB_2$) bind to the $CB_1$ and $CB_2$ receptors with nanomolar affinity in the radioligand assay (Figure 3A). A comparison of the binding of each individual diastereomer to the $CB_1$ and $CB_2$ receptors shows minimal selectivity (1.2–1.7x for $CB_2$) for binding to one receptor over the other. However, as shown in Figures 3B and 3C, **4a** (green triangle) binds both receptors with an affinity an order of magnitude higher than that of **4b** (blue circle), demonstrating stronger binding of the (9*R*)-HHC **4a** diastereomer. Of note, the

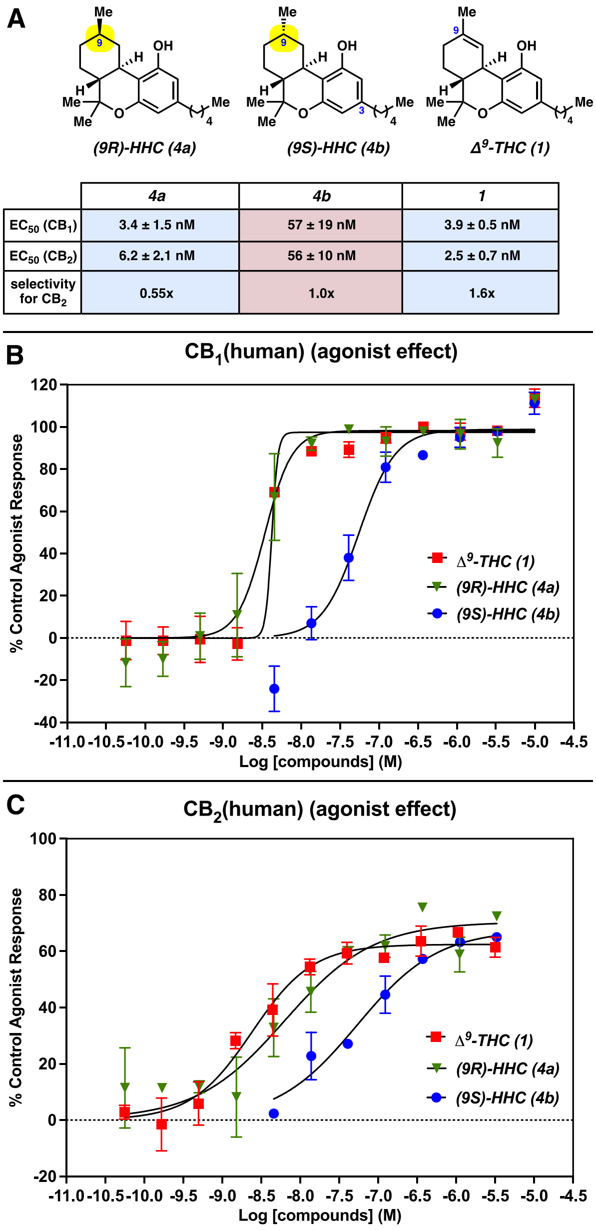


| | 4a | 4b | 1 |
|---|---|---|---|
| $K_i$ ($CB_1$) | 15 ± 0.8 nM | 176 ± 3.3 nM | 15 ± 4.4 nM |
| $K_i$ ($CB_2$) | 13 ± 0.4 nM | 105 ± 26 nM | 9.1 ± 3.6 nM |
| selectivity for $CB_2$ | 1.2x | 1.7x | 1.6x |

**Figure 3.** (A) Summary of radioligand binding affinity studies; error values represent the standard deviation. (B) Plotted inhibition of binding for human $CB_1$ cannabinoid receptor in transfected Chem-1 cell lysate after treatment with **1**, **4a**, and **4b**. (C) Plotted inhibition of binding for human $CB_2$ cannabinoid receptor in transfected CHO cell lysate after treatment with **1**, **4a**, and **4b**. For all experiments, data represent two replicate experiments, with error bars showing standard deviation (error bars omitted for clarity if the range is smaller than the data symbol), and the *Y*-intercept was constrained to zero, unless otherwise noted (see the SI for details).

binding affinity of **4a** (green triangle) is similar to that of $\Delta^9$-THC (**1**, red square) for both cannabinoid receptors.

The $CB_1$ and $CB_2$ functional assays were conducted using CHO cells transfected with human $CB_1$ and $CB_2$ cannabinoid receptors, respectively. Efficacy of the tested compounds was determined by measuring changes in cAMP concentrations relative to controls using homogeneous time-resolved fluorescence[45] (HTRF). In the functional assay, **4a** ($EC_{50}$ = 3.4 nM at $CB_1$ and 6.2 nM at $CB_2$) and **4b** ($EC_{50}$ = 57 nM at $CB_1$ and 56 nM at $CB_2$) demonstrated excitatory activity at the $CB_1$ and $CB_2$ receptors (Figure 4A). Of note, **4a** shows modest selectivity (1.8x) for $CB_1$ whereas there is no significant selectivity of **4b** between the $CB_1$ or $CB_2$ receptors. Figures 4B and 4C show that **4a** (green triangle) has 17- and 9-fold increases in potency, compared to **4b** (blue circle) for $CB_1$ and $CB_2$, respectively. This activity of **4a** (green triangle) is similar



| | 4a | 4b | 1 |
|---|---|---|---|
| $EC_{50}$ ($CB_1$) | 3.4 ± 1.5 nM | 57 ± 19 nM | 3.9 ± 0.5 nM |
| $EC_{50}$ ($CB_2$) | 6.2 ± 2.1 nM | 56 ± 10 nM | 2.5 ± 0.7 nM |
| selectivity for $CB_2$ | 0.55x | 1.0x | 1.6x |

**Figure 4.** (A) Summary of functional activity studies; error values represent the standard deviation. (B) Plotted response of human $CB_1$ receptor expressed in transfected CHO cells after treatment with **1**, **4a**, and **4b**, determined by measuring their effects on cAMP concentration. (C) Plotted response of human $CB_2$ receptor expressed in transfected CHO cells after treatment with **1**, **4a**, and **4b**, determined by measuring their effects on cAMP concentration. For all experiments, data represent two replicate experiments, with error bars showing the standard deviation (error bars omitted for clarity if the range is smaller than the data symbol) and the *Y*-intercept was constrained to zero unless otherwise noted (see the SI for details).

to that of $\Delta^9$-THC (**1**, red square). However, both HHCs **4a** and **4b**, such as $\Delta^9$-THC (**1**), are partial agonists of both receptors. Collectively, the results of the binding and functional assays demonstrate significant biological differences between HHC diastereomers **4a** and **4b**. These two diastereomers differ only in the directionality of the C9 methyl group, highlighting the effect of subtle structural modifications to the cannabinoid scaffold. These data also illustrate the need to understand the activity of individual compounds instead of mixtures, especially as new cannabinoids become available.

**Chemical Composition of HHC Products.** Given the different biological profiles of HHCs **4a** and **4b** described above, it is important to understand the chemical composition of recreational HHC products that are becoming increasingly widespread. We examined the online certificates of analysis for >60 HHC-containing products (see the SI for details). For 15 samples, the **4a**:**4b** ratios were not provided. For the others, the **4a**:**4b** ratios ranged from 0.2:1 to 2.4:1 (average of 1.4:1). As such, roughly 15%−70% of a given sample's HHC content is composed of the more potent isomer **4a**. This wide variability in chemical composition and the potential presence of heavy metals may have public health consequences.

Because catalytic hydrogenation of $\Delta^9$-THC (**1**) or $\Delta^8$-THC (**3**) is typically the final step in the synthesis of HHCs **4a** and **4b**, we questioned if consumer products had been analyzed for the heavy metals typically used for catalysis (i.e., Pd or Pt).[20,21] Numerous cannabis analytical laboratories were contacted in different states. Although testing for arsenic, mercury, lead, and cadmium is typically available as required by cannabis laws in most or all states, we learned that testing for Pd or Pt is rarely requested or offered at most cannabis analytical testing facilities. Several laboratories reiterated that such testing is not required. It was not possible for us to acquire and test commercial samples of HHC for heavy metals due to DEA regulations. We encourage that such testing be performed by HHC producers to ensure consumer safety, perhaps drawing from well-established practices for pharmaceutical production.

## ■ CONCLUSIONS

We have performed studies pertaining to HHCs **4a** and **4b**, which are emerging cannabinoids first synthesized in the 1940s. Our current study shows that HHCs **4a** and **4b** can be prepared using HAT reduction of $\Delta^9$-THC (**1**) or $\Delta^8$-THC (**3**), thus providing an alternative to classic hydrogenation conditions. This is notable, because the HAT reduction protocols provide **4a** as the major diastereomer, whereas classical hydrogenation conditions are less selective, leading to mixtures of isomers being available to consumers. Moreover, the traditional catalytic hydrogenation protocols, which bear significant safety risks, can be avoided. In addition, we have performed cannabinoid receptor studies of each diastereomer with $\Delta^9$-THC (**1**) as a control in the same assays. Both isomers **4a** and **4b** were shown to have partial $CB_1$ and $CB_2$ receptor agonist activity, such as $\Delta^9$-THC (**1**). However, isomer **4a**, accessed as the major diastereomer in the HAT reduction protocol, binds with higher affinity ($K_i$ = 15 and 13 nM at $CB_1$ and $CB_2$, respectively) and displays good activity in the functional assay ($EC_{50}$ = 3.4 and 6.2 nM at $CB_1$ and $CB_2$, respectively); the activity of isomer **4a** nearly matches that of $\Delta^9$-THC (**1**). This study demonstrates how minor modifications to the $\Delta^9$-THC (**1**) scaffold can lead to significant and varying differences in biological activity. Furthermore, the results of this study illustrate the importance of conducting assays on singular compounds in order to draw conclusions about how changes to the three-dimensional space in derivatives affect both their binding and potency. Lastly, this study shows that the method of $\Delta^9$-THC (**1**) reduction greatly affects the diastereomeric ratio of the HHC products formed. HAT provides an alternative method to access the more active (*9R*)-HHC isomer (**4a**) and could enable further biological evaluation. As highlighted in recent articles,[46−48] further studies of HHCs are desirable.

Although our scientific findings should not be used on their own to create federal or state policies, this study prompts many future directions that should be considered. For example, it would benefit society to increase the pace of chemical and biochemical-based research in the cannabinoid field while maintaining scientific rigor. New cannabinoids are emerging, and increased fundamental research is needed to characterize their in vitro and in vivo pharmacology and assess psychoactivity, therapeutic potential, and safety. In the U.S., this need has already been recognized by the federal government with recent efforts aimed at helping researchers secure faster approval to perform their research. However, more attention could be paid to the rising availability of new cannabis-derived compounds and analogs.[2,3]

With regard to specific research areas that require attention, we offer our view that organic and medicinal chemistry can play an important role in the cannabinoid research space. Historically, efforts by organic chemists to impact cannabinoid research have been instrumental. In this rapidly evolving climate, further engagement should be encouraged. Chemists can contribute by preparing new compounds using synthesis, semisynthesis, or biocatalysis, performing careful analyses of chemical composition and contaminants, conducting assays, investigating the mechanisms of action, performing structure-activity relationship studies, exploring receptor binding using computational studies, and ultimately engaging in advanced studies, such as clinical trials. Such efforts could help inform cannabis-based policies and regulations, ensure the safe and fair use of cannabinoids, and ultimately lead to the discovery of new medicines.

## ■ ASSOCIATED CONTENT

### SI Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acschembio.3c00254.

Detailed experimental procedures, compound characterization data, description of biological assays (PDF)

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### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

### Notes

The authors declare the following competing financial interest(s): N.K.G. has an equity interest and serves as an advisor for ElectraTect, Inc., a cannabinoid detection company.

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