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ENANTIOSELECTIVE SYNTHESIS AND PHARMACOLOGY OF 11-HYDROXY-(1'*S*,2'*R*)-DIMETHYLHEPTYL-Δ^8-THC

John Liddle and John W. Huffman*

Department of Chemistry, Clemson University, Clemson, SC 29634-1905, U.S.A.

Jenny L. Wiley and Billy R. Martin

Department of Pharmacology and Toxicology, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia 23298-0613, U.S.A.

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Abstract: An enantioselective synthesis of the (1'*S*,2'*R*)-dimethylheptyl cannabinoid side chain has been developed and employed in the synthesis of 11-hydroxy-(1'*S*,2'*R*)-dimethylheptyl-Δ^8-THC (**3**). Pharmacology, in vivo and in vitro, indicate (**3**) to be one of the most potent traditional cannabinoids known.

In the thirty years since Gaoni and Mechoulam described the isolation and elucidation of the structure of Δ^9-THC (Δ^9-tetrahydrocannabinol),[1] a comprehensive set of structure–activity relationships (SAR) for cannabinoids has been developed.[2] Such SAR have demonstrated that the cannabinoid side chain is an important pharmacophore. While the 1,2-dimethylheptyl (DMH) side chain is known to dramatically increase potency,[3] the 1,1-dimethylheptyl side chain is used almost exclusively in contemporary investigations. Not only are these cannabinoids very potent, but their precursor 1,3-dimethoxy-5-(1,1-dimethylheptyl)benzene is readily available, and no additional chiral centers are introduced.[4]

Recently, all four diastereoisomers of 1',2'-dimethylheptyl-Δ^8-THC were synthesized and the pharmacology of each isomer elucidated.[5] Although all four isomers are exceedingly potent, the (1'*S*,2'*R*)-isomer **1** has the greatest affinity for the cannabinoid brain (CB_1) receptor ($K_i = 0.46 \pm 0.04$) and is exceptionally potent in vivo. This isomer is significantly more potent than 1',1'-dimethylheptyl-Δ^8-THC (**2**) and consequently is the most potent traditional cannabinoid lacking a hydroxyl group at C-11, which has been reported to date. However, the synthesis included a tedious resolution of intermediate phenethylamides, requiring careful and repeated chromatography. In view of the potency of **1**, an enantioselective synthesis of the (1'*S*,2'*R*)-dimethylheptyl side chain has been developed and employed in the synthesis of 11-hydroxy-(1'*S*,2'*R*)-DMH-Δ^8-THC (**3**). The pharmacology, both in vivo and in vitro, of **3** has been determined. The synthesis was based on the method reported by Mechoulam et al. for the synthesis of 11-hydroxy-1',1'-DMH-Δ^8-THC (HU 210, **4**).[6] In this approach, the appropriately substituted resorcinol is condensed with 4-hydroxy-myrtenyl pivalate. The resulting cannabinoid pivalate ester is reduced to give **4** in high enantiomeric purity. Thus, the preparation of **3** called for a highly stereoselective synthesis of (2*S*,3*S*)-3-(3,5-

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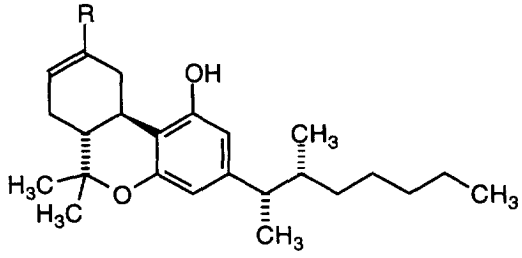
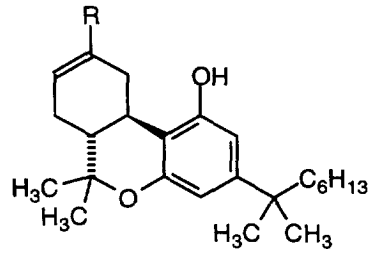
dimethoxyphenyl)-2-methylbutanoic acid (**5**) (Scheme 1), since this acid is readily converted to the resorcinol **6** using established procedures.[5]



1: R = CH_3
3: R = CH_2OH

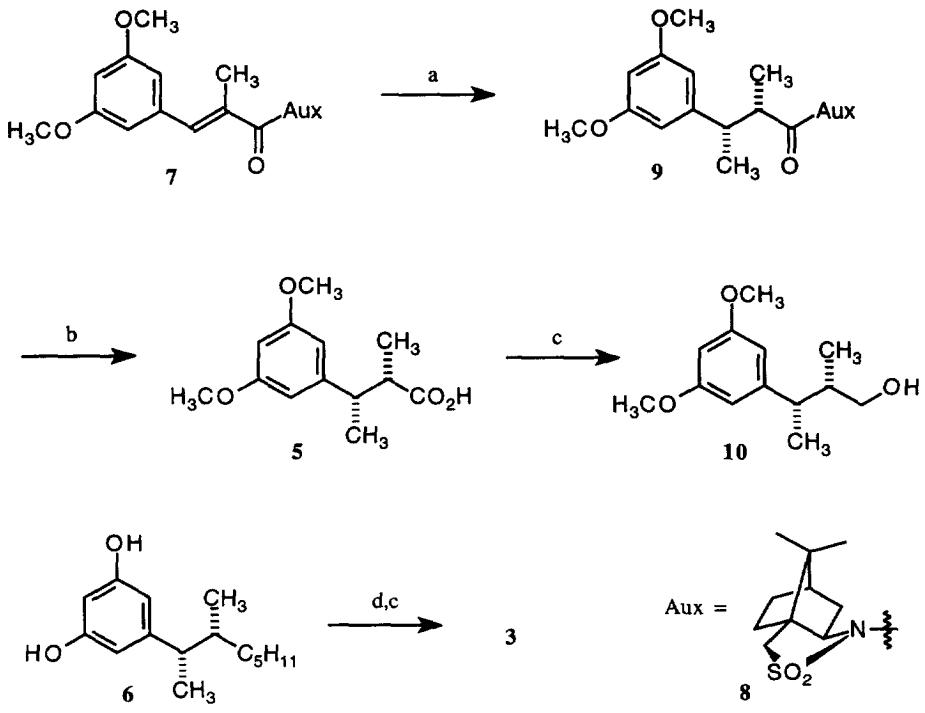


2: R = CH_3
4: R = CH_2OH (HU 210)

We reasoned that the two stereogenic centers of acid **5** would be developed via asymmetric conjugate addition of dimethylcopper lithium to a substrate which incorporates Oppolzer's chiral auxiliary.[7] *N*-[(*E*)-3-(3,5-dimethoxyphenyl)-2-methylpropenoyl]bornane-10,2-sultam (**7**) was prepared in 90% yield from (*E*)-3-(3,5-dimethoxyphenyl)-2-methylpropenoic acid[8] and auxiliary **8** according to the literature procedure.[9] Dimethylcopper lithium added smoothly to enoylsultam **7** in toluene at -40 °C to give, after quenching with saturated NH_4Cl/THF at -40 °C, a 94:2:2:2 mixture of diastereoisomers. The diastereoselectivity was determined by capillary GC-MS analysis of the crude reaction mixture. The major diastereoisomer (**9**) was isolated in 85% yield and >98% de by two recrystallizations from petroleum ether/ethyl acetate. Acylsultam **9** was homogeneous to capillary GC, ^1H and ^{13}C NMR. Mild saponification using LiOH in THF/H_2O furnished auxiliary **8** and acid **5** in quantitative yield. Reduction of **5** with $LiAlH_4$ gave primary alcohol **10** which was identical to material reported previously.[5] Homochiral alcohol **10** was converted to resorcinol **6** as described previously,[5] and **6** was condensed with 4-hydroxy-myrtenyl pivalate[10] in the presence of boron trifluoride etherate at -20 °C.[6] The resulting ester was reduced with lithium aluminum hydride to give cannabinoid **3** in 81% yield as a white solid.[11] Alcohol **10** and the 4-hydroxy-myrtenyl pivalate[6] employed in the synthesis of **3** are of >98% ee, and consequently the final cannabinoid **3** is of comparable optical purity.

The affinity of **3** for the cannabinoid brain receptor was determined by measuring its ability to displace a very potent cannabinoid, [^3H] CP-55,940, from its binding site in a membrane preparation as described by Compton et al.[12] Alcohol **3** was also evaluated in vivo in the mouse model of cannabimimetic activity[13,14] which includes measures of spontaneous activity (SA), antinociception (TF) and hypothermia (as rectal temperature, RT). The K_i values for cannabinoids **1–4** and their in vivo data are presented in Table 1.

Scheme 1



(a) Me_2CuLi/C_7H_8 then NH_4Cl/THF, -40 °C; (b) LiOH/H_2O/THF, 65 °C; (c) $LiAlH_4$/THF, 25 °C; (d) 4-Hydroxy-myrtenyl pivalate/$BF_3.Et_2O/CH_2Cl_2$, -20 °C.

Table 1. In vitro and in vivo pharmacology of cannabinoids **1–4**.

Compound	K_i (nM)	ED_{50} (μmol/kg)		
		SA	TF	RT
3	0.49 ± 0.08	0.01	0.03	0.02
(1'*S*,2'*R*)-DMH-Δ^8-THC (**1**)	0.46 ± 0.04	0.03	0.03	0.07
1',1'-DMH-Δ^8-THC (**2**)	0.77 ± 0.11[a]	0.27[a]	0.14[a]	0.15[a]
11–OH–1',1'-DMH-Δ^8-THC (**4**)	0.73 ± 0.11[b]	0.01[c]	0.02[c]	0.05[c]

[a]Martin, B. R.; Compton, D. R.; Semus, S. F.; Lin, S.; Marciniak, G.; Grzybowska, J.; Charalambous, A.; Makriyannis, A. *Pharmacol. Biochem. Behav.* **1993**, *46*, 295. [b]Ref. 12. [c]Little, P. J.; Compton, D. R.; Mechoulam, R.; Martin, B. R. *Pharmacol. Biochem. Behav.* **1989**, *32*, 661.

11-Hydroxy-(1'*S*,2'*R*)-dimethylheptyl-Δ^8-THC (**3**) is an exceedingly potent cannabinoid with affinity for the CB_1 receptor comparable to cannabinoid **1**, but is more potent in vivo than **1**, in accord with the established SAR for traditional cannabinoids. Cannabinoid **3** is similar in potency to HU 210 (**4**), the 1,1-dimethylheptyl

SAR for traditional cannabinoids. Cannabinoid **3** is similar in potency to HU 210 (**4**), the 1,1-dimethylheptyl analogue; however the increase in potency of **3** relative to **1** is not as great as that of **4** relative to **2**. In conclusion, a highly stereoselective synthesis of the (1*S*, 2*R*)-dimethylheptyl side chain has been developed making it a viable alternative to the readily available 1,1-dimethyl substituent.

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10. 4-Hydroxy-myrtenyl pivalate was prepared by a modification of the literature procedure. 3,5-dimethylpyrazole-chromium trioxide complex[15] was used to effect the allylic oxidation of myrtenyl pivalate. The oxo-myrtenyl pivalate was obtained in 55% yield which compares favorably with the 30% yield reported for the procedure using acetic acid in acetic anhydride.[6]
11. **3** was characterized by ^{1}H and ^{13}C NMR and gave acceptable HRMS data. Purity was established by TLC and ^{13}C NMR. **3** has mp 143–145 °C and $[\alpha]_D$ -206.5° (*c* 0.9, $CHCl_3$).
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