Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 7, No. 21, pp. 2799-2804, 1997

0960-894X/97 $17.00 + 0.00

PII: S0960-894X(97)10086-5

SYNTHESIS AND PHARMACOLOGY OF THE 1′,2′-DIMETHYLHEPTYL-Δ^8-THC ISOMERS: EXCEPTIONALLY POTENT CANNABINOIDS

John W. Huffman* and Sammy G. Duncan, Jr.

Department of Chemistry, Clemson University, Clemson, SC 29634-1905 ,USA

Jenny L. Wiley and Billy R. Martin

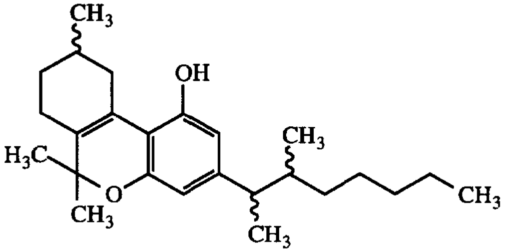
Department of Pharmacology and Toxicology, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia 23298-0613, USA

Abstract: The four diastereomers of 1′,2′-dimethylheptyl-Δ^8-THC (**2**) have been synthesized. Pharmacology both in vitro and in vivo indicated that all four isomers were very potent cannabinoids. The 1′*R*,2′*S* and 1′*S*,2′*R* are considerably more potent than the other two isomers, and are among the most potent traditional cannabinoids known. © 1997 Elsevier Science Ltd.

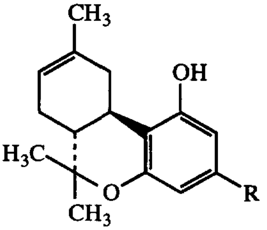
During the development of structure–activity relationships (SAR) for cannabinoids, it was found that a mixture of the eight isomeric 3-(1,2-dimethylheptyl)-$\Delta^{6a,10a}$-tetrahydrocannabinols (DMHP, **1**) were extremely potent cannabinoids.[1] In 1968, Aaron and Ferguson described the synthesis of the eight individual isomers, using classical methodology and separation techniques.[2] In addition to animal pharmacology, these isomers were administered intravenously to human subjects, and it was found that two of them showed marked hypotensive behavior.[3] The human experiments, and the effects of these isomers in animals has been summarized, and in all cases it was found that Aaron and Ferguson's "isomers 2 and 4" were the most potent.[1c] Subsequently, both Petrzilka et al.[4] and Mechoulam's group[5] reported the synthesis of the stereoisomeric mixtures of 3-(1′,2′-dimethylheptyl)-Δ^8 (**2**) and Δ^9-THC. The pharmacology of these mixtures was reported, and both were found to be very potent cannabinoids.[5]

Although the 1′,2′-dimethylheptyl cannabinoids are recognized as being exceedingly potent, the 1′,1′-dimethylheptyl analogues are 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.[6] In view of the acknowledged potency of the 1′,2′-dimethylheptyl cannabinoids, and the presence of two chiral centers in the side chain, the synthesis of the four individual diastereomers of 3-(1′,2′-dimethylheptyl)-Δ^8-THC (**2**) has now been carried out and both the relative and absolute stereochemistry of each has been clearly defined.[7] Also, the pharmacology of each isomer, both in vivo and in vitro has been evaluated. The synthesis of the isomers of **2** was based upon the method employed for the synthesis of the isomeric 1′- and 2′-methyl-Δ^8-THCs.[8] In this approach, an appropriately substituted hydrocinnamic acid is synthesized, resolved and the remaining atoms of the side chain added via a modified

Kochi coupling. The resulting dimethyl ether is converted to the resorcinol, and subjected to a Petrzilka synthesis to provide the target cannabinoid.[8]



1



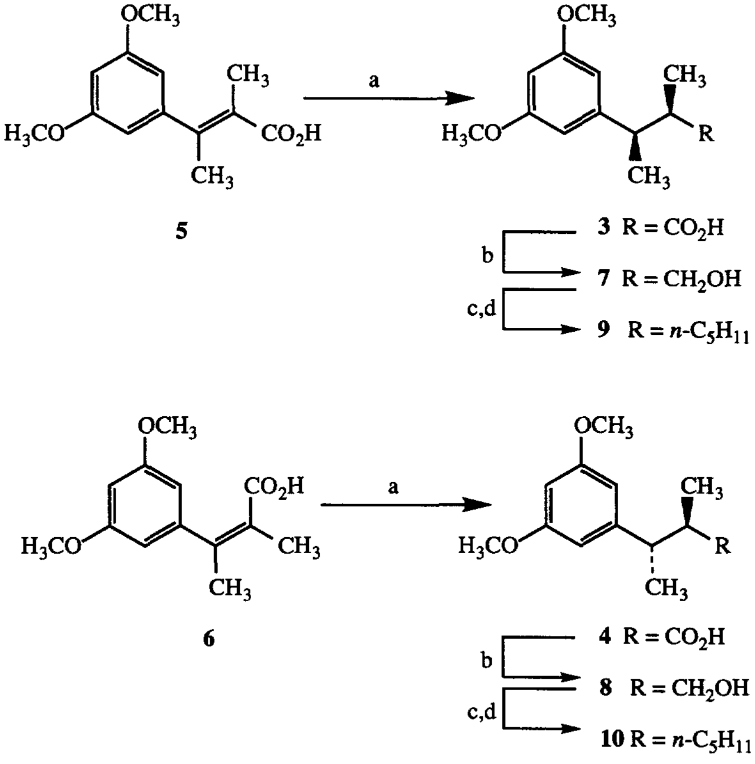
2 R = $CH(CH_3)CH(CH_3)(CH_2)_4CH$
11 R = n-C_5H_{11}

For the synthesis of the isomers of **2**, the *threo* (2*R**,3*S**, **3**) and *erythro* (2*R**,3*R**, **4**) isomers of 3-(3,5-dimethoxyphenyl)-2-methylbutanoic acid (Scheme 1) were needed. These acids are available via stereospecific hydrogenation of the *E*-(**5**) and *Z*-(**6**) isomers, respectively, of 3-(3,5-dimethoxyphenyl)-2-methyl-2-butenoic acid.[2] Acids **5** and **6** were prepared previously in poor yield by a Reformatsky reaction, followed by crystallization of the dicyclohexylamine salts; however, a more attractive approach, the Horner–Emmons reaction of 3,5-dimethoxyacetophenone with triethyl 2-phosphonopropionate (Scheme 1), gave a 1.7 to 1 mixture of the ethyl esters of **5** and **6** in 60% yield. Hydrolysis of the ester of **5** using KOH provided acid **5** in 44% yield, while acid **6** was obtained in 67% yield by aqueous LiOH hydrolysis of the corresponding ester.[9] The physical properties of acids **5** and **6** were consistent with those reported previously.[2] Catalytic hydrogenation of these acids afforded hydrocinnamic acids **3** and **4**, respectively, in quantitative yield, the properties of which were consistent with those reported by Aaron and Ferguson.[2]

Initial attempts to effect the resolution of acids **3** and **4** were patterned on those employed successfully in the resolution of the acid precursors to 1′- and 2′-methyl-Δ^8-THC.[8] Conversion of the acids to the corresponding amides with *S*-(–)-α-phenethylamine was carried out using the conditions of Miyazawa (hydroxybenztriazole, DCC) to avoid epimerization.[10] The secondary amides, which were separated by careful and repeated chromatography, were obtained in yields of 29% to 66%.[11] The diastereomeric amides were obtained as crystalline solids which were homogeneous to ^1H and ^{13}C NMR.[12] The absolute stereochemistry was determined by X-ray crystallography of the *S*-phenethylamides derived from the 2*R*,3*R*-enantiomer of **3**, and the 2*R*,3*S*-enantiomer of **4** (isomers depicted in Scheme 1).

The phenethylamides employed as intermediates in the synthesis of 1′- and 2′-methyl-Δ^8-THC were converted to the carboxylic acids by dissolving metal reduction to the primary amide, followed by cleavage with Na_2O_2 under carefully controlled conditions.[8] Although the phenethylamides derived from **3** and **4** were smoothly converted to the primary amides, the primary amides were completely resistant to hydrolysis under a variety of conditions. Reduction of racemic **3** and **4** to the corresponding alcohols (racemic **7** and **8**),[11] and attempted resolution using a variety of procedures was equally unsuccessful.[13] The cleavage of the primary amides was finally accomplished by conversion to the corresponding imino ether using trimethyloxonium tetrafluoroborate, followed by heating with aqueous $NaHCO_3$.[14] The acids obtained by this procedure were very difficult to purify, and were reduced directly to the primary alcohols, 3-(3,5-dimethoxyphenyl)-2-methyl-1-butanol (**7**, **8**, only the 2*R*,3*R* and 2*R*,3*S* enantiomers depicted), which were identical except for optical rotation to the racemic alcohols.[15] The pure primary alcohols were obtained in four steps from the phenethylamides in overall yields of 19% to 35%.

Scheme 1



(a) H_2(g)/10% Pd(C)/EtOH/48 psi; (b) $LiAlH_4$/THF, 25 °C; (c) TsCl/C_5H_5N/$CHCl_3$, 0 °C; (d) *n*-BuMgCl/Li_2CuCl_4/THF

The balance of the synthesis followed the methodology employed in the synthesis of the 1′- and 2′-methyl analogues of Δ^8-THC.[8] Conversion of the isomeric alcohols to the corresponding *p*-toluenesulfonate esters, followed by modified Kochi coupling with *n*-butylmagnesium chloride in the presence of Li_2CuCl_4 provided 2-

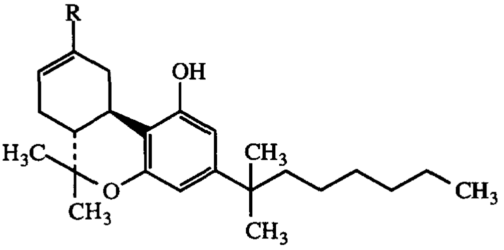
(3,5-dimethoxyphenyl)-3-methyloctane (**9**, **10**, only the 2*R*,3*S* and 2*S*,3*S* enantiomers, respectively, depicted).[11,16] The unoptimized yields from alcohols **7** and **8** to ethers **9** and **10** ranged from 23% to 53% for two steps. Isomer **9** is the (–)-*threo* compound described by Aaron and Ferguson, while **10** is the (+)-*erythro* isomer.[2,17] The synthesis of the four stereoisomers of cannabinoid **2** was completed in 35% to 46% yield by conversion of ethers **9** and **10** to the corresponding resorcinols (BBr_3), and acid catalyzed condensation with *trans-p*-menthadienol.[8,11]

The affinity of the four isomers of **2** for the cannabinoid brain receptor was determined measuring their ability to displace a very potent cannabinoid, [^{3}H] CP-55,940, from its binding site in a membrane preparation as described by Compton et al.[18] The K_i values for **2**, Δ^8-THC and the 1′,1′-dimethylheptyl analogue of **2** are presented in Table 1. These compounds were also evaluated in vivo in a mouse model of cannabimimetic activity.[19,20] These evaluations include measures of spontaneous activity (SA), antinociception (TF), hypothermia (as rectal temperature, RT). These data for the isomers of **2**, Δ^8-THC (**11**) and the 1′,1′-dimethylheptyl analogue of **2** (Δ^8-THC-1,1-DMH, **12**) are also included in Table 1.

Table 1. In vitro and in vivo pharmacology of the isomers of 1′,2′-dimethylheptyl-Δ^8-THC (**2**), Δ^8-THC, and 1′1′-dimethylheptyl-Δ^8-THC.

Compound	K_i (nM)	ED_{50} (μmol/kg)		
		SA	TF	RT
2-1′*R*,2′*S*	0.60 ± 0.15	0.04	0.10	0.07
2-1′*S*,2′*R*	0.46 ± 0.04	0.03	0.03	0.07
2-1′*S*,2′*S*	0.81 ± 0.08	0.12	0.18	0.19
2-1′*R*,2′*R*	0.84 ± 0.21	0.45	0.42	0.63
Δ^8-THC (**11**)	44 ± 12[a]	2.9[a]	4.5[a]	4.8[a]
Δ^8-THC-1,1-DMH (**12**)	0.77 ± 0.11[a]	0.27[a]	0.14[a]	0.15[a]
11–OH–Δ^8-THC-1,1-DMH (**13**)	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] Reference 18. [c] Little, P. J.; Compton, D. R.; Mechoulam, R.; Martin, B. R. *Pharmacol. Biochem. Behav.* **1989**, *32*, 661.



12 R = CH_3
13 R = CH_2OH

Although all four isomers of 1′,2′-dimethylheptyl-Δ^8-THC are exceedingly potent cannabinoids, the 1′*R*,2′*S*, and 1′*S*,2′*R* isomers have somewhat greater affinity for the CB1 receptor, and are considerably more potent in vivo than the 1′*S*,2′*S*, and 1′*R*,2′*R* epimers. The 1′*R*,2′*S*, and 1′*S*,2′*R* isomers are also significantly more potent than Δ^8-THC-1,1-DMH (**12**) and approach 11-hydroxy-Δ^8-THC-1,1-DMH (HU-210, **13**) in potency. Δ^8-THC-1,1-DMH (**12**) is the most potent traditional cannabinoid lacking a hydroxyl group at C-11 reported previously, and the 1′*R*,2′*S*, and 1′*S*,2′*R* isomers of **2** exceed **12** in activity. At this point there does not appear to be an adequate rationalization for the difference in potency between the isomeric pairs of 1′,2′-dimethylheptyl-Δ^8-THC, however, these differences are probably due to subtle conformational differences in the epimers.

Of the eight isomers of **1** synthesized by Aaaron and Ferguson, two, "isomers 2 and 4" were found to be significantly more potent than the other six.[1c,2,3] These are the isomers of **1** derived from (–)-*threo* and (+)-*threo*-7-(3,5-dimethoxyphenyl)-6-methyloctane, which are the 6*S*,7*R*- and 6*R*,7*S*-isomers, respectively, of ether **9**, which give rise to the 1′*R*,2′*S*- and 1′*S*,2′*R*-epimers of cannabinoid **2**. The other two *threo* isomers of **1**, differ in stereochemistry at C-9 from the more potent epimers.[2] The stereochemistry at this center has been shown to have a marked effect upon cannabinoid activity.[21]

Although two of the epimers of cannabinoid **2** are considerably more potent than Δ^8-THC-1,1-DMH (**12**), they are much more difficult to prepare, and unless and until a convenient and highly stereoselective synthesis of one of them, preferably the more potent 1′*S*,2′*R* isomer, is developed, the 1′,2′-dimethyl side chain is not a viable alternative to the readily available 1′,1′-dimethyl substituent.

Acknowlegements. The work at Clemson was supported by grant DA03590, and that at The Medical College of Virginia, Virginia Commonwealth University by grant DA03672, both from the National Institute on Drug Abuse. High resolution mass spectral data were determined by the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois. We thank Drs. William T. Pennington and George Schimek, Clemson University, for the X-ray crystallographic studies, and Dr. Paul Consroe, Department of Pharmacology, University of Arizona for calling our attention to some of the early studies of these cannabinoids.

References and Notes

1. (a) Adams, R.; MacKenzie, S.; Loewe, S. *J. Am. Chem. Soc.* **1948**, *70*, 644. (b) Adams, R.; Harfenist, M.; Loewe, S. *J. Am. Chem. Soc.* **1949**, *71*, 1624. (c) Pradhan, S. *Neurosci. Biobehav. Rev.* **1984**, *8*, 369 presents a detailed review of the pharmacology of these stereoisomeric mixtures. (d) Razdan, R. K. *Pharmacol. Rev.* **1986,** *38,* 75.
2. Aaron, H. S.; Ferguson, C. P. *J. Org. Chem.* **1968,** *33*, 684.
3. Siddell, F. R.; Pless, J. E.; Neitlich, H.; Sussman, P.; Copelan, H. W.; Sim, V. M. *Proc. Soc. Exp. Biol. Med.* **1973**, *142*, 867.
4. Petrzilka, T.; Haefliger, W.; Sikemeier, C. *Helv. Chim. Acta* **1969**, *52*, 1102.
5. Edery, H.; Grunfeld, Y.; Porath, G.; Ben-Zvi, Z.; Shani, A.; Mechoulam, R. *Arzneim. Forsch.* **1973**, *22*, 1995.

6. Dominianni, S. J.; Ryan, C. W.; DeArmitt, C. W. *J. Org. Chem.* **1977**, *42*, 344.
7. The workers in ref 2 correctly assigned the relative stereochemistry to the chiral centers in the side chain, but did not determine the absolute stereochemistry.
8. Huffman, J. W.; Lainton, J. A. H.; Banner, W. K.; Duncan, S. G.; Jordan, R. D.; Yu, S.; Dai, D.; Martin, B. R.; Wiley, J. L.; Compton, D. R. *Tetrahedron*, **1997**, *53*, 1557.
9. Patel, D.; VanMiddlesworth, F.; Danabuaer, J.; Gannett, P.; Sih, C. *J. Am. Chem. Soc.* **1986**, *61*, 606. Attempted hydrolysis of the *Z* ester using KOH gave partial conversion to the *E* isomer.
10. Miyazawa, T.; Yamada, T.; Kuwata, J. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 606.
11. All new compounds were characterized by ^{1}H and ^{13}C NMR and gave either acceptable analytical or HRMS data. Purity was established by TLC and ^{13}C NMR.
12. Each diastereomeric amide has a characteristic set of ^{1}H NMR signal for the various methyl protons.
13. These unsuccessful resolution studies are described in the Ph.D. dissertation of S. G. Duncan, Jr., Clemson University, August, 1997.
14. Hanessian, S. *Tetrahedron Lett.* **1967**, 1549.
15. The *R,R* enantiomer of **7** has $[\alpha]_D$ –20.7°; *S,S*, $[\alpha]_D$ 20.5°; *S,R* enantiomer of **8**, $[\alpha]_D$ 12.5°; *R,S*, $[\alpha]_D$ –10.6°. Within the limits of detection by ^{1}H and ^{13}C NMR, **7** and **8** were pure liquids.
16. In ethers **9** and **10** the priority sequence for denoting stereochemistry is the reverse of that in the previous compounds in which an oxygen is present at the future C-3'.
17. For ethers **9**, *R,S* $[\alpha]_D$ –32.8° (lit.[2] –36.2°); *S,R* $[\alpha]_D$ 31.9° (lit.[2] 36.9°). For ethers **10**, *S,S* $[\alpha]_D$ 3.6° (lit.[2] 3.0°); *R,R* $[\alpha]_D$ –5.3° (lit.[2] –3.2°). The specific rotations carried out in this work are all in $CHCl_3$ solution, those in ref 2 were determined as neat liquids.
18. Compton, D. R.; Rice, K. C.; De Costa, B. R.; Razdan, R. K.; Melvin, L. S.; Johnson, M. R.; Martin, B. R. *J. Pharmacol. Exp. Ther.* **1993**, *265*, 218.
19. (a) Martin, B. R.; Compton, D. R.; Little, P. J.; Martin, T. J.; Beardsley, P. M. In *Structure–Activity Relationships in Cannabinoids*; Rapaka, R. S.; Makriyannis, A., Eds.; NIDA Research Monograph 79, National Institute on Drug Abuse: Rockville, 1987; pp 108–122. (b) Little, P. J.; Compton, D. R.; Johnson, M. R.; Melvin, L. S.; Martin, B. R. *J. Pharmacol. Exp. Ther.* **1988**, *247*, 1046.
20. Compton, D. R.; Gold, L. H.; Ward, S. J.; Balster, R. L.; Martin, B. R. *J. Pharmacol. Exp. Ther.* **1992**, *263*, 1118.
21. (a) Reggio, P. H.; Greer, K. V.; Cox, S. M. *J. Med. Chem.* **1989**, *32*, 1630. (b) Huffman, J. W.; Banner, W. K.; Zoorob, G. K.; Joyner, H. H.; Reggio, P. H.; Martin, B. R.; Compton, D. R. *Tetrahedron*, **1995**, *51*, 1017.

(*Received in USA* 29 *August* 1997; *accepted* 29 *September* 1997)