

Bioorganic & Medicinal Chemistry Letters 8 (1998) 2223-2226

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

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.

Received 22 June 1998; accepted 14 July 1998

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. © 1998 Elsevier Science Ltd. All rights reserved.

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 (CB₁) receptor (K_i = 0.46 ± 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 4hydroxy-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 (2S,3S)-3-(3,5dimethoxyphenyl)-2-methylbutanoic acid (5) (Scheme 1), since this acid is readily converted to the resorcinol 6 using established procedures.⁵



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 acid⁸ 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 NH₄Cl/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 ¹³C NMR. Mild saponification using LiOH in THF/H₂O furnished auxiliary **8** and acid **5** in quantitative yield. Reduction of **5** with LiAlH₄ 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 pivalate¹⁰ 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 pivalate⁶ 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.



(a) Me₂CuLi/C₇H₈ then NH₄Cl/THF, -40 $^{\circ}$ C; (b) LiOH/H₂O/THF, 65 $^{\circ}$ C; (c) LiAlH₄/THF, 25 $^{\circ}$ C;

(d) 4-Hydroxy-myrtenyl pivalate/BF_3.Et_2O/CH_2Cl_2, -20 $^\circ C.$

 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}	0.27ª	0.14 ^a	0.15 ^a
$11-OH-1', 1'-DMH-\Delta^8-THC$ (4)	0.73 ± 0.11^{b}	0.01°	0.02 ^c	0.05 ^c

^aMartin, B. R.; Compton, D. R.; Semus, S. F.; Lin, S.; Marciniak, G.; Grzybowska, J.; Charalambous, A.; Makriyannis, A. *Pharmacol. Biochem. Behav.* **1993**, *46*, 295. ^bRef. 12. ^cLittle, 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 CB₁ 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 (1S, 2R)-dimethylheptyl side chain has been developed making it a viable alternative to the readily available 1,1-dimethyl substituent.

Acknowledgments. 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.

References and Notes

- 1. Gaoni, Y.; Mechoulam, R. J. Am. Chem. Soc. 1964, 86, 1646.
- 2. Razdan, R. K. Pharmacol. Rev. 1986, 38, 75.
- Edery, H.; Grunfeld, Y.; Porath, G.; Ben-Zvi, Z.; Shani, A.; Mechoulam, R. Arzneim. Forsch. 1973, 22, 1995.
- 4. Dominianni, S. J.; Ryan, C. W.; DeArmitt, C. W. J. Org. Chem. 1977, 42, 344.
- 5. Huffman, J. W.; Duncan, S. G.; Wiley, J. L.; Martin, B. R. Bioorg Med. Chem. Lett. 1997, 7, 2799.
- 6. Mechoulam, R.; Lander, N.; Breuer, A.; Zahalka, J. Tetrahedron: Asymmetry 1990, 1, 315.
- 7. Oppolzer, W.; Kingma, A. J.; Poli, G; Tetrahedron 1989, 45, 479.
- 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. Oppolzer, W.; Poli, G.; Kingma, A. J.; Starkemann, C.; Bernardinelli, G. Helv. Chim. Acta 1987, 70, 2201.
- 10. 4-Hydroxy-myrtenyl pivalate was prepared by a modification of the literature procedure. 3,5dimethylpyrazole-chromium trioxide complex¹⁵ 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
- 3 was characterized by ¹H and ¹³C NMR and gave acceptable HRMS data. Purity was established by TLC and ¹³C NMR. 3 has mp 143-145 °C and [α]_D -206.5° (c 0.9, CHCl₃).
- 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.
- (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.
- Compton, D. R.; Gold, L. H.; Ward, S. J.; Balster, R. L.; Martin, B. R. J. Pharmacol. Exp. Ther. 1992, 263, 1118.
- 15. Salmond, W. G.; Barta, M. A.; Havens, J. L. J. Org. Chem. 1978, 43, 2057.