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VARIATION OF THE ALKYL SIDE CHAIN IN Δ^8-THC

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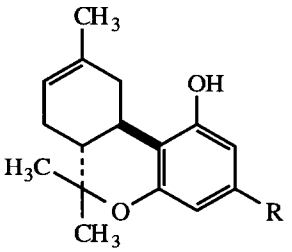
Summary

The synthesis of (2'*RS*)-2'-methyl-, (3'*RS*)-, (3'*S*)-3'-methyl-, and 4'-methyl-Δ^8-THC has been carried out, and the pharmacology of all four compounds has been investigated. All four compounds showed typical cannabinoid activity both *in vitro* and *in vivo*. The 2'-methyl compound is somewhat more active than Δ^8-THC, while the 4'-methyl isomer is less active. The 3'-methyl-Δ^8-THC has approximately the same activity as the parent cannabinoid.

Key Words: 2'-methyl-Δ^8-THC, 3'-methyl-Δ^8-THC, 4'-methyl-Δ^8-THC

Although a considerable body of data exists which relates the structural features of cannabinoids with their biological activity, little is known concerning the effect of a single methyl substituent on the five carbon alkyl side chain of Δ^8- or Δ^9-tetrahydrocannabinol (THC) (1). It is known in the case of synthetic cannabinoids which contain a seven carbon side chain, that the addition of two methyl substituents, either both at C-1' or at C-1' and C-2' leads to greatly enhanced cannabinoid activity (1).



1 R = $CH_2CH(CH_3)CH_2CH_2CH_3$
2 R = $CH_2CH_2CH(CH_3)CH_2CH_3$
3 R = $CH_2CH_2CH_2CH(CH_3)_2$

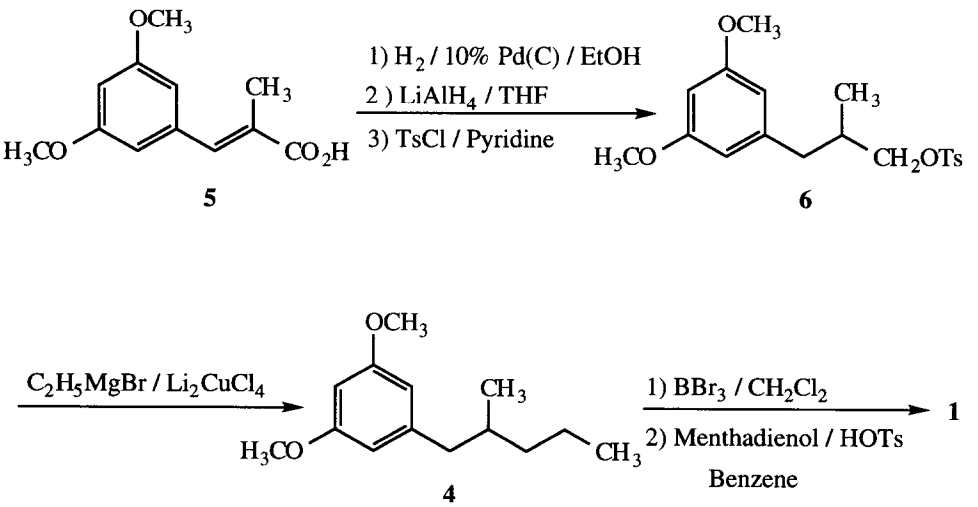
Some years ago, Mechoulam's group reported that 1'-methyl-THC derivatives were less active than the unsubstituted analogues in both the Δ^8- and Δ^9-series (2), however, there have been no reports of the effects of methyl substitution at other positions on the side chain. We have undertaken the synthesis of 2'-, 3'- and 4'-methyl-Δ^8-THC [**1**- **3**] in order to examine in a systematic way the effect of these alkyl substituents on the cannabimimetic activity of this isomer of THC. The pharmacology of Δ^8- and Δ^9-THC is quite similar, and the choice was made to employ the Δ^8-isomers due to their relative ease of synthesis, and their enhanced stability relative

to their Δ^9 counterparts. All of the Δ^8-THC analogues which are described below were synthesized by a variation of the classical Petrzilka synthesis, in which a 3-alkyl resorcinol is reacted with *trans*-menthadienol in the presence of *p*-toluenesulfonic acid (3). The overall synthetic challenge then became the synthesis of the requisite alkyl resorcinol, which in all cases was prepared from the corresponding dimethyl ether by cleavage with boron tribromide.

Synthetic Chemistry

Racemic 1-(3,5-dimethoxyphenyl)-2-methylpentane [**4**] was prepared from commercially available 3,5-dimethoxybenzaldehyde by a five step sequence as depicted in Scheme 1. Initial Horner-Emmons condensation with triethyl 2-phosphonopropionate proceeded with simultaneous ester hydrolysis to provide the E-α-methyl cinnamic acid [**5**]. The acid was sequentially hydrogenated, reduced (lithium aluminum hydride) and converted into *p*-toluenesulfonate ester **6**, which was reacted with ethylmagnesium bromide in the presence of Li_2CuCl_4 to give 1-(3,5-dimethoxyphenyl)-2-methylpentane [**4**]. Ether cleavage, followed by condensation with menthadienol gave 2'-methyl-Δ^8-THC [**1**] as a mixture of diastereomers at C-2'. Efforts are being made to obtain pure stereoisomers by resolution of the hydrogenated cinnamic acid.

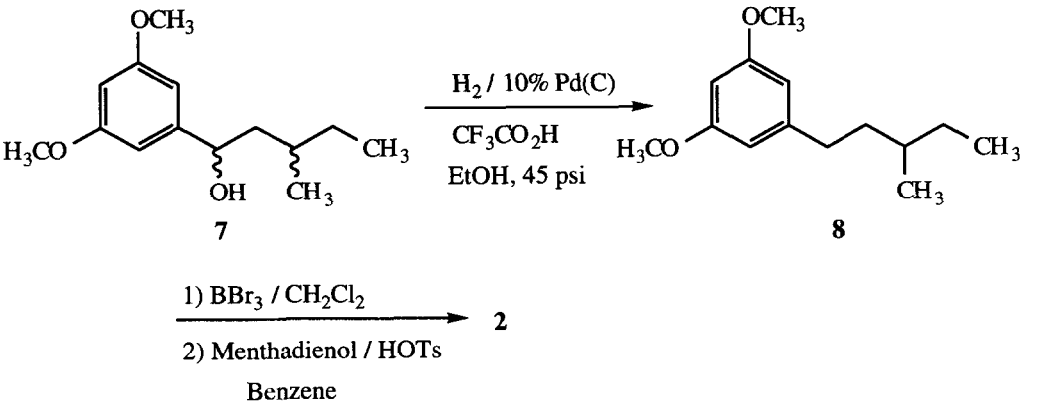
Scheme 1



The 3'-methyl analogue was synthesized by initially carrying out a Grignard reaction between racemic 2-methylbutylmagnesium bromide and 3,5-dimethoxybenzaldehyde as shown in Scheme 2.

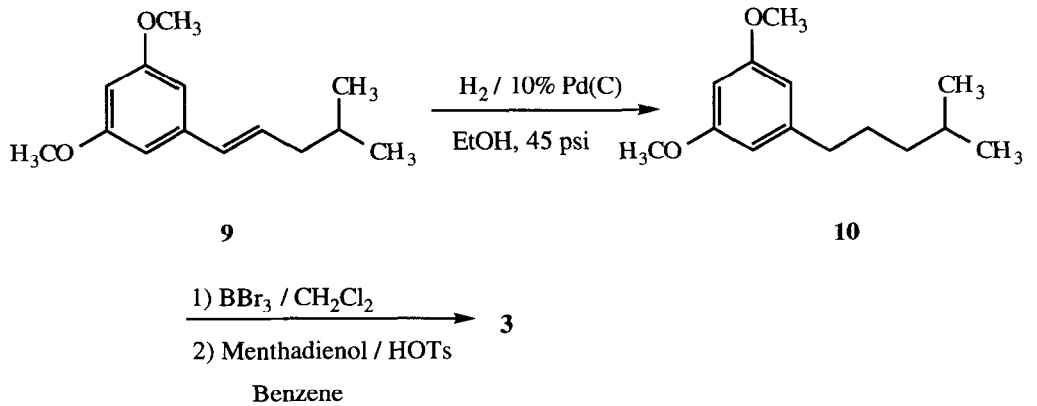
The alkyl bromide which served as the precursor for the Grignard reagent was prepared by the reaction of 2-methyl-1-butanol with phosphorus tribromide. The mixture of diastereomeric benzylic alcohols [**7**] was reduced to 1-(3,5-dimethoxy)-3-methylpentane [**8**] by prolonged treatment with hydrogen in the presence of a palladium catalyst and trifluoroacetic acid. Ether cleavage, followed by acid catalyzed reaction with menthadienol provided 3'-methyl-Δ^8-THC [**2**] as a mixture of diastereomers at C-3'. An identical reaction sequence was carried out using commercially available (*S*)-(+)-1-bromo-2-methylbutane to provide (3'*S*)-3'-methyl-Δ^8-THC.

Scheme 2



4'-Methyl-Δ^8-THC [**3**] was prepared from 3,5-dimethoxybenzaldehyde by initial Wittig reaction with the ylide derived from *i*-amyltriphenylphosphonium bromide (Scheme 3). The mixture of stereoisomeric substituted styrenes (**9**, only the E-isomer is shown) was reduced to 1-(3,5-dimethoxyphenyl)-4-methylpentane [**10**]. The usual sequence of ether cleavage, followed by condensation with menthadienol provided the target cannabinoid.

Scheme 3



Pharmacology

The pharmacology of the Δ^8-THC analogues was evaluated *in vitro* by measuring their ability to displace the very active cannabinoid, CP-55,940 from its binding site in a membrane preparation (K_I) (4). The *in vivo* pharmacology of the cannabinoids was evaluated using the mouse tetrad model which measures spontaneous activity (SA), antinociception using the tail flick procedure (TF), decrease in rectal temperature (RT) and catalepsy as determined by the ring immobility method (RI) (4). The results for the analogues of Δ^8-THC described above are summarized in Table I. Data for Δ^8-THC are included for comparison. Some of these data are preliminary, however it is apparent that all of these compounds bind to the cannabinoid receptor, and all show typical cannabinoid pharmacology *in vivo*.

Both the *in vitro* and *in vivo* data indicate that 2'-methyl-Δ^8-THC is a more active cannabinoid than Δ^8-THC, however since the compound as evaluated is a mixture of diastereomers at C-2' it is not possible at this time to comment on the relationship between the stereochemistry of the methyl group and biological activity. The 3'*RS*- and 3'*S*-methyl compounds show similar binding affinity for the cannabinoid receptor, and the values are very similar to that of Δ^8-THC. The *in vivo* data for the 3'-*S*-isomer are very similar to those of Δ^8-THC, but the *RS* mixture shows significantly less activity for hypothermia and catalepsy. A resolution of these differences must await the preparation of the 3'-*R* isomer.

TABLE I

Pharmacology of Δ^8-THC Analogues

Compound	K_I(nM)	ED_{50} (μ moles/kg)			
		SA	TF	RT	RI
Δ^8-THC	44±12	2.9	4.8	4.5	4.8
$CH_2CH(CH_3)CH_2CH_2CH_3$ [**1**]	13	61% at 0.9	1	3	3
$CH_2CH_2CH(CH_3)CH_2CH_3$ [**2**]	54±18	3	1	30	50
S-$CH_2CH_2CH(CH_3)CH_2CH_3$ [**2**]	41	9	0.6	3° at 9.2	6
$CH_2CH_2CH_2CH(CH_3)_2$ [**3**]	141±52	3	1	30	30

4'-Methyl-Δ^8-THC shows somewhat less affinity for the cannabinoid receptor than Δ^8-THC, but is an active cannabinoid. The *in vivo* activity is in the same range as that of the parent cannabinoid in spontaneous activity and antinociception, but it is less active in measurement of hypothermia and catalepsy.

Conclusions

These data indicate that substitution by a methyl group at C-2' leads to enhanced activity, while a 3'*S*-methyl has little effect on activity. The 4'-methyl analogue is less active than the parent cannabinoid. At this point questions remain concerning the effect of stereochemistry at C-2' and C-3'. In order to resolve these questions regarding stereochemistry, work in progress is designed to prepare samples of 2'*R*- and 2'*S*-2'-methyl-Δ^8-THC, as well as 3'*R*-3'-methyl-Δ^8-THC.

Acknowledgements

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