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SYNTHESIS OF THE INDIVIDUAL, PHARMACOLOGICALLY DISTINCT, ENANTIOMERS OF A TETRAHYDROCANNABINOL DERIVATIVE

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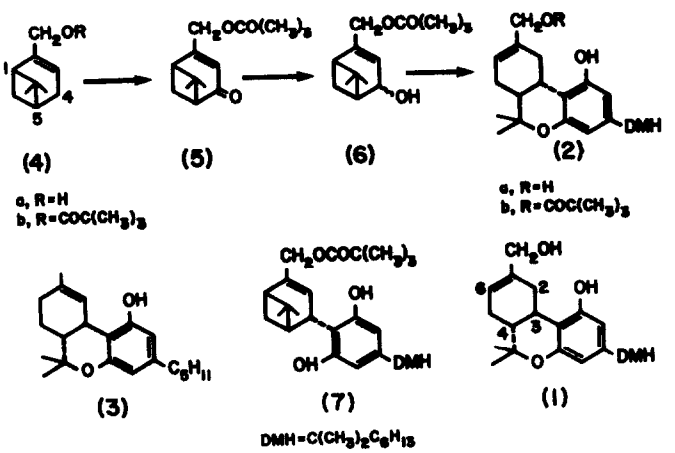
Abstract The individual enantiomers of the 1,1-dimethylheptyl homolog of 7-hydroxy- Δ^6-tetrahydrocannabinol, (1) and (2a), which exhibit distinct pharmacological profiles, have been obtained with very high e.e. by synthesis from the antipodes of myrtenol.

The 1,1-dimethylheptyl (DMH) homolog of [3R,4R]-7-hydroxy- Δ^6-tetrahydrocannabinol (1) is a very potent psychotropic agent with a hashish type (cannabimimetic) profile of activity. Depending on the animal test used, it is 70-800 times more potent than the natural [3R,4R]- Δ^1-tetrahydrocannabinol ([3R,4R]-Δ^1- THC) (3).[1] By contrast the DMH homolog of [3S,4S]-7-hydroxy-Δ^6-THC (2a) shows practically no cannabimimetic activity (as measured in four different

laboratories) in various animal tests in doses up to several thousand times higher than the ED_{50} of the [3R,4R] enantiomer (1).[1] However (2a) prevents vomitting in pigeons, treated with the strongly emetic anticancer drug cisplatin.[2] It also acts as a functional N-methyl-D-asparate (NMDA) receptor blocker It binds to sites distinct from those of other non-competitive NMDA antagonists.[3] It is also a potent blocker of NMDA-induced tremor, seizures and lethality in mice,[3] and may therefore prove useful as a drug against NMDA-receptor mediated neurotoxicity. These results indicate that non-cannabimimetic THC-type compounds with [3S,4S] configuration have considerable therapeutic potential.

We report now the synthesis of (1) and (2a). A central aim of our approach was to achieve very high e.e. in order to make possible eventual therapeutic use of the [3S,4S] enantiomer, as the presence of traces of the [3R,4R] enantiomer could lead to undesirable side effects. The synthesis follows an approach previously used by us for the preparation of (3).[4] The few THC-type enantiomeric pairs synthesized so far have not shown high pharmacological stereospecifity;[5] however their e.e have not been reported, and are presumably not higher than the e.e. of their starting materials (92-98% in the case of α-pinene used in the synthesis of THC)



[1S,5R]-Myrtenol (4a), $[\alpha]_D$ + 47 5 (neat), obtained by oxidation of commercial α-pinene, (Aldrich), $[\alpha]_D$ + 50.7 (neat), was esterfied with pivalyl chloride to the ester (4b) which, on oxidation with anhydrous sodium chromate, at 35°C for 72 hours in acetic acid-acetic anhydride gave, after chromatography on silica gel, 4-oxo-myrtenyl pivalate (5), 30%, m.p. 42-43 (from pentane); $[\alpha]_D$ + 165 ($CHCl_3$); λ max (EtOH) 250 nm (ε 6000); ϑ max ($CHCl_3$) 1730 and 1670 cm^{-1}; δ ($CDCl_3$) 4.72 (CH_2-O), 5.84 (C=CH). Reduction of (5) with lithium tri-tert-butoxyaluminohydride in dry tetrahydrofuran led to 4-hydroxy-myrtenyl pivalate (6) which, without further purification, was condensed with 5-(1,1-dimethylheptyl)-resorcinol in dry methylene chloride in the presence of boron trifluoride etherate at -20°C. Silica gel chromatography (elution with 10% ether in petroleum ether) gave predominantly the pivalate ester (2b), 50%. Compound (2b) presumably is formed through the intermediate (7), which can be isolated if the condensation reaction is done with p-toluene sulphonic acid, rather than with boron trifluoride etherate. Reduction of (2b) with lithium aluminum hydride led to (2a), 96%, m.p. 141-2°C (from pentane), $[\alpha]_D$ + 227 ($CHCl_3$), δ ($CDCl_3$) 6.40, 6.25 (2 arom H's), 5.6 (C=CH), 4.09 (CH_2-O) The same reaction sequence, starting with commercial [1R,5S]-myrtenol (Aldrich) $[\alpha]_D$ - 57.7 , (neat) gave (1), m.p. 141-2°C, $[\alpha]_D$ -226 ($CHCl_3$). The enantiomeric purity of thrice recrystallized (1) and (2a) was established by h p l c analysis of the diastereoisomeric bis (MTPA) esters obtained by reaction with (S)-+)-α-methoxy-α-(trifluoromethyl) phenyl-acetyl (MTPA) chloride [6] The e.e. of (1) and (2a) was found to be higher than 99.8% [7] This high degree of enantiomeric purity is evidenced also by their distinct binding to a cannabinoid receptor . compound (1) binds with an affinity circa 1500 times higher than the

enantiomeric (2a).[8] The sharply contrasting pharmacologic behavior of (1) and (2a) mentioned above is also indicative of their enantiomeric purity. The high e.e. achieved is probably due to the easy crystallization of the intermediate oxo-esters (5, in the synthesis of 2a) and of the final products (1 and 2a). The Δ^1 isomer of (1) has recently been prepared via a different synthetic route.[9]

The above results show that [3S,4S]-THC-type compounds (such as 2a) can be obtained with very high e.e. and can thus be regarded as promising pharmaceutical entities.[10]

References and Notes

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7. H.p l.c.: column, 250-4 LiChrospher Si 60 (5 um) cartridge (Merck, Germany); solvent, 95:5 n-hexane.ethyl acetate; flow, 1 ml/min; detector (uv) 270 nm. Bis (MPTA) ester of (1):Rt, 12 5 min; bis (MPTA) ester of (2a):Rt, 15.6 min. N.m r. $\delta(CDCl_3)$:bis (MPTA) ester of (1), 3.52, 3.78 (2 OCH_3 groups); bis (MPTA) ester of (2), 3.53, 4.50 (2 OCH_3 groups)
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