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Synthesis of a labelled terpene synthon, useful in the preparation of metabolites of Δ^1-tetrahydrocannabinol*

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SUMMARY

The synthesis of an isotopically labelled terpene synthon (**4**) is described. The usefulness of this terpene synthon in the synthesis of Δ^1-THC metabolites is shown by preparation of (±)-[$^2H_{10}$]-Δ^1-THC-7-oic acid (**5**) by condensation of **4** with [$^2H_7$]-olivetol. Compound **5** is suitable as internal standard for mass spectrometric assays.

Key words: (±)-[$^2H_3$]-terpene synthon, (±)-[$^2H_{10}$]-Δ^1-THC-7-oic acid, Cannabis, Synthesis

INTRODUCTION

Preparations of the plant *Cannabis sativa* L. are among the most widely used illegal drugs today. Δ^1-Tetrahydrocannbinol (Δ^1-THC), the major psychoactive constituent of Cannabis, undergoes an extensive metabolism in the body and is transformed to more polar substances before being excreted [1]. Δ^1-THC-7-oic acid has proved to be the major urinary metabolite of Δ^1-THC in man, accounting for about 1/3 of the urinary metabolites [2]. The high potency of Δ^1-THC and the vast number of metabolites formed have contributed to the difficulties involved in elucidating the metabolic pathways.

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A great deal of information as yet to be unearthed as to the metabolism of Δ^1-THC in man, including inter- and intraindividual variation, as well as sex differences. These sorts of investigations require the use of molecules labelled with deuterium (^{2}H), tritium (^{3}H), or carbon-14 (^{14}C). Such labelled materials also have a place in forensic medicine as chemical references and internal standards in the separation and identification of acidic urinary metabolites of Δ^1-THC. Different analytical techniques are applied, depending on the number of samples, the type and concentrations of substance to be analyzed, and the purpose of the analysis [3]. Urine analysis based on immunoassays, e.g. RIA and EIA, which measure the presence of Δ^1-THC-7-oic acid, are at present most commonly used. These techniques are time saving but often non-specific, and more selective techniques are required for confirmation of positive results. Mass spectrometry is the method of choice for confirmation, and selected ion monitoring can be used with deuteriumlabelled Δ^1-THC-7-oic acid as internal standard for quantification. Several synthetic strategies have been developed for the synthesis of Δ^1-THC and its metabolites, e.g. 7-hydroxy-Δ^1-THC and Δ^1-THC-7-oic acid [4-8]. An important finding was reported by Uliss *et al.* in the synthesis of 7-hydroxy-Δ^1-THC, showing that the isomerization of the labile double bond in the Δ^1-position was conveniently prevented by introduction of a 1,3-dithiane moiety into the molecule [9].

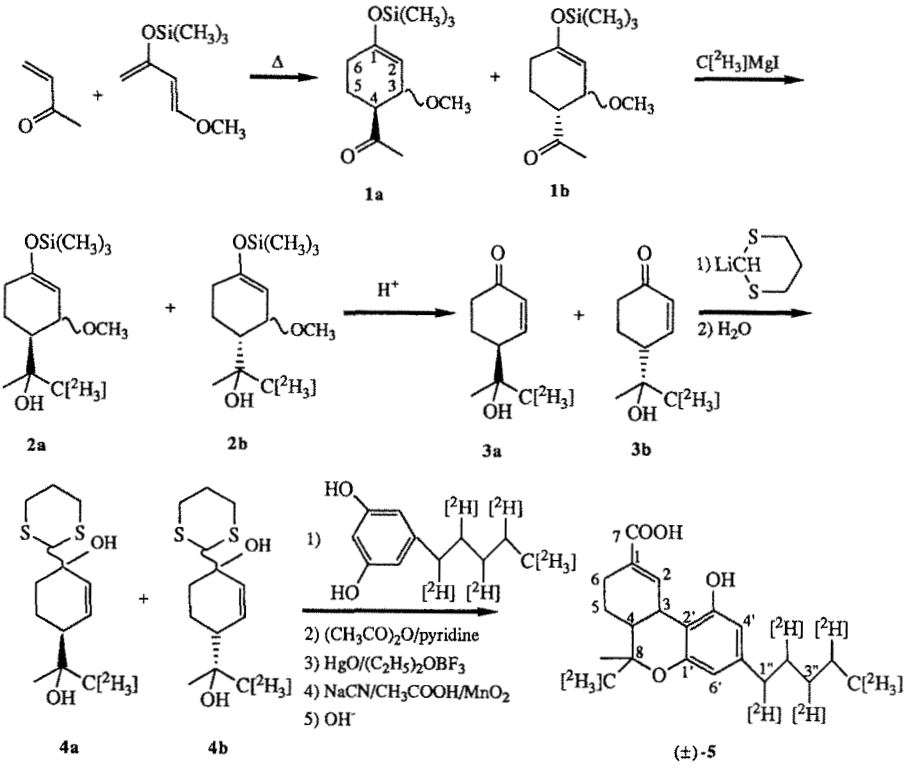
The aim of the present study was to propose a method for the synthesis of a labelled terpene synthon (**4**; Figure 1) and to show its usefulness in the preparation of labelled metabolites of Δ^1-THC, demonstrated by the synthesis of (±)-[$^2H_{10}$]-Δ^1-THC-7-oic acid (**5**). The synthetic route described readily allows the introduction of deuterium, tritium or carbon-14 into the molecule. This can be utilized, with only minor changes in the reaction sequence, in the preparation of other metabolites of THC in the Δ^1-series.

EXPERIMENTAL

[$^2H_3$]-Methyl iodide (99 atom% ^{2}H) was obtained from Janssen Chimica, Belgium. 1-Methoxy-3-(trimethylsilyloxy)-1,3-butadiene and 3-buten-2-one was purchased from Aldrich, Europe. Melting points were determined on a Digital melting point apparatus (Electrothermal) and are uncorrected. UV was measured on a Varian Uv -Vis spectrophotometer, model 635. ^{1}H-NMR and ^{13}C-NMR were recorded at room temperature (20°C) on a Varian VXR-400 instrument at 399.95 MHz and 100.56 MHz or a Varian Gemini 300 spectrometer at 300.075 MHz and 75.462 MHz, respectively. Spectra were recorded with TMS as the internal standard

in $CDCl_3$, unless otherwise stated. Two-dimensional NMR spectroscopy was performed with standard COSY and C-H heteronuclear correlation. APT was used to determine the carbon multiplicity. Resolution enhancement was used for the determination of coupling constants. Mass spectroscopic analyses were carried out using either a Finnigan TSQ70-MAT triple quadropole instrument (equipped with a Finnigan-MAT thermospray source, interphase and controller; ammoniumsulfate was used as the ionizing agent) or an LKB model 2091-051 GC/MS (EI) operated at 50 eV. For gas chromatography (GC) a Varian Aerograph Model 2100 equipped with a flame ionization detector was used with: oven 110°C, injector/detector 150°C, carrier gas (N_2) 25 ml/min, H_2 25 ml/min, O_2 200 ml/min. The glass column (1.7 m x 2 mm i.d.) was packed with 3 % Silicone SE-30 on Gas-Chrom Q (100-125 mesh). Before GC and

Figure 1. Reaction scheme for the synthesis of deuterium labelled terpene synthon (**4**), and its use in the preparation of (±)-[$^2H_{10}$]-Δ^1-THC-7-oic acid (**5**) [**1a**=(S,R)+(R,R); **1b**=(S,S)+(R,S)].



MS analyses the esterified endproduct (**5**) was further derivatized by silylation with N,O-bis(trimethylsilyl)-acetamide in dry acetonitrile. Merck Silica gel 60 F_{254} plates with 0.2 mm layer thickness on aluminium sheets were employed for thin layer chromatography (TLC).
All synthetic and analytical operations were initially performed with unlabelled compounds, and the structures of unlabelled intermediates and products were confirmed spectroscopically.

(±)-1-(1,3-dithiane-2-yl)-4-(1-hydroxy-1-[$^2H_3$]-methyl-ethyl)-cyclohex-2-en-1-ol (**4**)

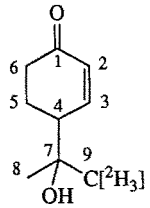
1-Methoxy-3-(trimethylsilyloxy)-1,3-butadiene (10 g; 52.2 mmole) was mixed with 3-buten-2-one (4.83 ml; 58.0 mmole) and heated at 90°C to give four isomers (**1a** and **1b**; Figure 1). The reaction was monitored on TLC (1:4 diethyl ether-petroleumether; R_f(**1**)=0.21; 0.27) and on GC (R_t(**1**)=8.9 min; 11.6 min). After 4 hours the reaction mixture was cooled in ice and the crude product was used in the subsequent step without any further treatment.
^{1}H-NMR ($CDCl_3$, no TMS was added as internal standard. Instead shifts were related to the solvent signal) **1a+1b** δ 5.04; 4.86 (d, *J*=5.4 Hz, 1H; br s, 1H, H-2), 4.04-4.12 (m, 2H, H-3), 3.17; 3.14 (s, 3H; s, 3H, -O$\underline{C}H_3$), 2.48-2.57; 2.27-2.35 (m, 1H; m, 1H, H-4), 2.10; 2.06 (s, 3H; s, 3H, -CO$\underline{C}H_3$), 1.51-2.03 (n.r., 8H, H-5+H-6), 0.09; 0.07 (s; s, 18H, -OSi($\underline{C}H_3$)$_3$). ^{13}C-NMR ($CDCl_3$, no TMS was added as internal standard. Instead shifts were related to the solvent signal) **1a+1b** δ 210.2; 208.2 (-$\underline{C}OCH_3$), 156.1; 152.9 (C-1), 101.0; 103.0 (C-2), 76.3; 73.4 (C-3), 55.3; 55.2 (-O$\underline{C}H_3$), 51.8; 51.7 (C-4), 29.5; 27.6 (-CO$\underline{C}H_3$), 29.4; 28.7 (C-6), 22.7; 18.5 (C-5), 0.0 (-OSi($\underline{C}H_3$)$_3$).

To a suspension of 1.55 g Mg and 1.0 ml (16.0 mmole) [$^2H_3$]methyl iodide in 40 ml dry diethyl ether, 3.0 ml (47.9 mmole) [$^2H_3$]methyl iodide in 40 ml dry diethyl ether was added slowly under stirring in order to maintain reflux. The solution was heated at about 40°C for an additional 20 min, transferred to a dropping funnel and added dropwise to the mixture of **1a** and **1b** dissolved in 50 ml dry diethyl ether. Vigorous stirring was needed since a yellow solid appeared during the addition. After heating at about 40°C for 20 min the reaction was quenched by dropwise addition of methanol (6.8 ml) and saturated aqueous NH_4Cl (40 ml). Water was added to dissolve the residue and the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried with Na_2SO_4, filtered and evaporated *in vacuo* to give a orange-red oil. Two major products were visualized on TLC (1:4 diethyl ether-petroleumether; R_f(**2**)=0.14; 0.23) and one major peak was seen on GC (R_t(**2**)=13.3 min).

Without further purification a 1% solution (200 ml) of CCl_3COOH in saturated aqueous ethyl acetate was added to the mixture under stirring at room temperature. After one hour water was added and the organic phase was washed with 1% aqueous NH_3-solution to neutral pH. The aqueous phase was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over Na_2SO_4 and filtered, giving a red oil upon evaporation *in vacuo*. The mixture was chromatographed on silica gel 60 (70-230 mesh, Merck) with a gradient of ethyl acetate-toluene (0-30%) giving **3** as a yellow oil (TLC: 100% diethyl ether, R_f(**3**)= 0.39; GC: R_t(**3**)=4.0 min, UV: 10 mg/ml (EtOH), λ_{max}=227 mμ, ε=9610). The overall yield was about 60% based on the amount of 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene used. MS m/z 175 $[M+NH_4]^+$, 158 $[M+H]^+$. The isotopic distribution according to mass spectrometry was, m/z (172-175): 172, 1.5%; 175, 98.5%. ^{1}H-NMR and ^{13}C-NMR ($CDCl_3$) data in Table 1.

Table 1: ^{1}H- and ^{13}C-NMR chemical shifts of (±)-4-(1-hydroxy-1-[$^2H_3$]methyl-ethyl)-cyclohex-2-en-1-one (**3**), in $CDCl_3$, δ-units relative to internal TMS.

Position	^{1}H-Chemical shift (δ)	Multiplicity		Coupling constants J (Hz)		^{13}C-Chemical shift (δ)
1						200.7
2	6.02	ddd	(1H)	2,3	10.4	130.3
				2,4ax	2.8	
				2,6eq	1.1	
3	7.14	dt	(1H)	3,4ax	2	152.7
				3,5eq	2	
4ax	2.41-2.47	n.r.	(1H)			47.7
5ax	1.70	dddd	(1H)	5ax,5eq	13.1	24.5
				5ax,4ax	11.3	
				5ax,6eq	4.3	
5eq	2.10	ddddd	(1H)	5eq,4ax	5	
6ax	2.32	ddd	(1H)	6ax,6eq	16.6	37.3
				6ax,5ax	14.2	
				6ax,5eq	5	
6eq	2.49	dddd	(1H)	6eq,5eq	3	
7						71.9
8	1.16[b]	s	(2H)			25.7[b]
9	1.25[b]	s	(1H)			28.0[b]
OH[a]	2.64	br s	(1H)			



(3)

a) hydroxylic proton shifts vary with concentration, temperature, and solvent
b) = shift values are interchangeable
n.r. = not sufficiently resolved

To a solution of 3.47 g (28.1 mmole) 1,3-dithiane dissolved in 100 ml dry tetrahydrofuran, 11.2 ml (28.1 mmole) *n*-butyllithium was added dropwise under stirring and under nitrogen

atmosphere at -45°C. After 2 hours at -30°C the reaction mixture was cooled to -45°C before dropwise addition of 4.01 g (25.5 mmole) **3** in 35 ml dry tetrahydrofuran. The temperature was allowed to rise to room temperature before storage at +4°C overnight. Water was added to the crude mixture, which was then washed with an aqueous saturated NH_4Cl solution and extracted with diethyl ether, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The procedure used is based on the work of Corey *et al.* [10]. The resulting oil was purified on silica gel 60 eluting with a gradient of 0-40% ethyl acetate-toluene (TLC: 100% diethyl ether, R_f(**4**)=0.44). White crystalls of **4**, in about 40% yield, were formed after recrystallization from ethyl acetate, m.p. 116.6-117.2°C (cf. unlabelled **4** m.p. 119.1-119.5°C, litt. [9] 116-117°C). MS m/z 295 $[M+NH_4]^+$, 277 ($[M+NH_4]^+$-H_2O), 260 ($[M+H]^+$-H_2O). The isotopic distribution according to mass spectrometry was, m/z (292-295): 294, 4.9%; 295, 95.1%. ^{1}H-NMR and ^{13}C-NMR ($CDCl_3$) data in Table 2.

[$^2H_{10}$]-Δ^1-THC-7-oic acid (**5**)

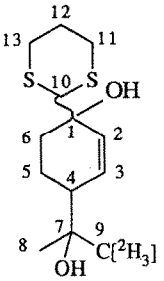
1 Eq. [$^2H_7$]-olivetol, synthesized by Ohlsson *et al.* [11], was mixed with 1 eq. **4** in benzene and heated to 40°C in the presence of 0.1 eq. of CH_3SO_3H as a catalyst. The reaction was quenched by addition of a 5% NaOH solution. The aqueous phase was extracted with diethyl ether and the combined organic layers were washed with water, dried over Na_2SO_4 and evaporated to dryness. The desired compound was purified in about 20% yield from a mixture containing abnormal-THC, diadducts and other products on Florisil (1:19 diethyl ether-petroleumether).

The phenolic group was acetylated with acetic acid anhydride in pyridine (1:3) at room temperature as described by Handrick *et al.* [12].The reaction mixture was poured into ice water and extracted with diethyl ether. The combined extracts were repeatedly washed with small portions of 2N HCl, aqueous saturated $NaHCO_3$ and brine and then dried over Na_2SO_4 as well as by azeotropic distillation with benzene.

The 1,3-dithiane masking group was hydrolyzed according to a procedure described by Handrick *et al.* [12] using red HgO in 15% aqueous tetrahydrofuran and BF_3-Et_2O. The acetylated condensation product dissolved in tetrahydrofuran was added dropwise. After 20 min. at room temperature diethyl ether was added and washed with a solution of saturated

Table 2: ^{1}H- and ^{13}C-NMR chemical shifts of (±)-1-(1,3-dithiane-2-yl)-4-(1-hydroxy-1-[$^{2}H_3$]-methyl-ethyl)-cyclohex-2-en-1-ol (**4**), in $CDCl_3$, δ-units relative to internal TMS.

Position	^{1}H-Chemical shift (δ)	Multiplicity		Coupling constants J (Hz)		^{13}C-Chemical shift (δ)
1						72.9[b]
2	5.91	ddd	(1H)	2,3	10.4	133.3
				2,4ax	2.3	
				2,6eq	1.2	
3	5.98	dd	(1H)	3,4ax	2.8	131.4
4ax	2.14-2.20	m	(1H)			46.2
5ax	1.57-1.70	n.r.	(1H)			21.4
5eq	1.80-1.93	n.r.	(1H)			
6ax	1.57-1.70	n.r.	(1H)			32.9
6eq	2.37-2.44	m	(1H)			
7						72.8[b]
8	1.20[c]	s	(2H)			26.7[c]
9	1.25[c]	s	(1H)			28.3[c]
10	4.29	s	(1H)			58.8
11ax;13ax	2.86	ddt	(2H)	ax,eq	14	30.5;30.8
				ax,12ax	11	
				ax,12eq	3	
11eq;13eq	2.93	ddd	(2H)	eq,12eq	5	
				eq,12ax	4	
12ax	1.80-1.93	n.r.	(1H)			25.8
12eq	2.08	dtt	(1H)	eq,ax	14	
7-OH[a]	2.50[b]	s	(1H)			
1-OH[a]	1.56[b]	s	(1H)			



(**4**)

aqueous $NaHCO_3$. The aqueous phase was extracted with diethyl ether and washed once with water and brine.

The aldehyde obtained was dissolved in methanol and oxidized by a procedure based on the work of Corey *et al.* [13]. NaCN and acetic acid was added under stirring and the pH was carefully controlled to be neutral. MnO_2 was added and the pH was checked again. For the reaction to take place it is crucial to keep the pH neutral. After filtration the residue was concentrated and the acetylated Δ^1-THC-7-oic acid was hydrolyzed under basic conditions using KOH in water-ethanol as described by Pitt *et al.* [14]. The reaction mixture was extracted with diethyl ether. The aqueous phase was acidified with 2N HCl and extracted again with diethyl ether. The organic layers were dried over Na_2SO_4 and evaporated after filtration.

For simplification in the chromatographic procedure, using straight phase, **5** was esterified with diazomethane in order to obtain the methylester and purified by preparative TLC (Silica gel 60 F_{254} plates on glass) with 1:4 diethyl ether-petroleumether as eluent, developed three times. The overall yield, from the condensation between **4** and [$^2H_7$]-olivetol, to the endproduct (±)-**5** was in the range of 5-10%. The spectral data were in accordance with previously published data for unlabelled Δ^1-THC-7-oic acid [2, 14].

MS of TMS-**5** as methylester, m/z (rel. intensity) 440 ([M]$^+$, 43%), 425 ([M]$^+$-CH_3, 28%), 381 ([M]$^+$-$COOCH_3$, 69%), 362 ([M]$^+$-[$^2H_7$]-pentyl sidechain, 24%), 73 (TMS, 100%). The isotopic distribution according to mass spectrometry was, m/z (359-369): 365, 1.1%; 366, 4.6%; 367, 15.1%; 368, 33.8%; 369, 44.9%.

^{1}H-NMR ($CDCl_3$) **5** as methylester δ 7.98 (d, J=2 Hz, 1H, H-2), 6.27 (s, 1H, H-6'), 6.14 (s, 1H, H-4'), 3.74 (s, 3H, -COO$\underline{C}H_3$), 3.36 (br d, 1H, H-3), 1.72 (dt, J=12 Hz, 1H, H-4), 1.43; 1.11 (s; s, 3H, gem-$\underline{C}H_3$).

^{13}C-NMR ($CDCl_3$) **5** as methylester δ 168.3 (C-7), 154.9 (C-1'), 154.1 (C-3'), 143.3 (C-5'), 142.6 (C-2), 129.1 (C-1), 110.1 (C-6'), 107.5 (C-4'), 106.9 (C-2'), 51.7 (-COO$\underline{C}$H3), 44.3 (C-4), 34.4 (C-3), 27.4 (gem-$\underline{C}H_3$), 25.4 (C-6), 24.3 (C-5), 19.1 (gem-$\underline{C}H_3$).

RESULTS AND DISCUSSION

The increasing demand for selective and sensitive techniques in the quantification of urinary metabolites of Δ^1-THC in forensic investigations has prompted the development of strategies for the synthesis of reference compounds as well as internal standards [3, 15].

The usefulness of the synthesis of [$^2H_3$]-terpene synthon (**4**, Figure 1) discussed here is demonstrated by the preparation of (±)-[$^2H_{10}$]-Δ^1-THC-7-oic acid (**5**).

Synthesis of **1a** and **1b** was based on the work of Danishefsky *et al.* [16] giving a 1:1 mixture according to GC and ^{1}H-NMR data of the (SS+RR) and (SR+RS) isomers (Figure 1). No attempts were made to separate the four isomers.

The labelled isotope was introduced into the molecule in the conversion of the keto function in **1** to the tertiary alcohol in compound **2** using a labelled Grignard reagent prepared from deuterium labelled methyl iodide. Carbon-14 labelled methyl iodide has been used in the same manner in order to obtain a radiolabelled terpene synthon. Another possibility is to label the molecule using a tritiated Grignard reagent. Treatment of **2** with a dilute solution of

trichloroacetic acid resulted in the diastereoisomers **3a** and **3b**. The introduction of deuterium into the molecule creates a second chiral center at C-7 (see fig. Table 1). This shows in the proton NMR as two singlets around 1.1-1.3 ppm, corresponding to three protons altogether. The intensity of the peaks (2:1) shows the relative proportions of the diastereoisomers. In the carbon-13 NMR spectrum the signals from the carbons with deuterium bound to them appear as two septets with a dramatic reduction in intensity at an upfield shift of about 0.8 ppm. Finally, addition of the anion of 2-lithio-1,3-dithiane to **3** was performed largely according to Corey *et al.* [10] but at a somewhat lower temperature, -45°C, giving the labelled terpene synthon (**4**). The introduction of the 1,3-dithiane group prevents the double bond from isomerizing in the following condensation rection. The enhanced stability of Δ^1-isomers is attributed to electronic effects caused by the neighbouring sulfur atoms [9]. A detailed presentation of proton- and carbon-13 NMR data, not previously reported for compounds **3** and **4**, is given in Tables 1 and 2.

To enable a high deuterium content with a minimum of unlabelled compound, for use as internal standard for quantification in selected ion mass spectrometry, we used [$^2H_7$]-olivetol in the condensation with **4**. This reaction, clearly the limiting step for the overall sequence, has been the target of further improvements. Unfortunately, although various conditions have been examined, no major improvement has been achieved in this particular step. The hydrolysis of the 1,3-dithiane group was performed according to Handrick *et al.* [12]. However, the reaction time was reduced from 3 h to 20 min. Another critical reaction, besides the condensation, is the oxidation of the α,β-unsaturated aldehyde, after removal of the dithiane masking group, to the carboxylic acid (**5**). Limitations arise in the choice of how to perform the reaction, since one has to be careful not to cause isomerization of the double bond to the thermodynamically more stable Δ^6-position, which occurs if conditions are too acidic [5]. The use of Pitt's conditions [14], with acetone cyanohydrin and manganese dioxide in the oxidation step of the aldehyde, failed to give **5** in our hands. Instead we performed the reaction according to a description by Corey *et al.* [13]. Keeping the reaction mixture at a neutral pH was important in order to get the desired product, (±)-[$^2H_{10}$]-Δ^1-THC-7-oic acid (**5**). The isotopic purity was determined by mass spectrometry showing that the content of unlabelled compound is less than 0.5% in the deuterium labelled final product, indicating that the label is stable throughout the reactions.

Hitherto, several reports on the synthesis of labelled Δ^1-THC have been presented but only a

very limited number on labelled THC metabolites. Most positions in the THC molecule have been labelled, including the side-chain, the aromatic ring, the allylic positions, the 3 position and the geminal methyl groups [11, 17-27]. Syntheses of different olivetol analogues, labelled with carbon-14, tritium or deuterium, have been reported. The carbon-14 isotope has been introduced into the olivetol molecule both in the aromatic ring [17, 18] and in the side-chain [28]. Several olivetol analogues labelled with deuterium have been prepared, all of which have the label in the side-chain [11, 20-23, 29]. The preparation of tritium labelled olivetol has also been described [19, 20]. In addition to this, Hoellinger *et al.* [22] have synthesized 4', 5'-dehydroolivetol which after condensation with a suitable terpene could be deuterated or tritiated. Molecules labelled in the side-chain or in the aromatic part are not suitable as tracers in metabolic studies, due to loss of the isotopes in the metabolic process. This is not a problem when the labelled molecules are to be used as internal standards in quantitative measurements. The method and the conditions chosen (e.g. mass spectrometry, EI or CI) for the quantification could instead be the limiting factor in the choice of suitable labelled molecules. The only report, to our knowledge, on the synthesis of any labelled Δ^1-THC metabolites is of the preparation of 7-hydroxy-Δ^1-THC-[$^2H_3$] by Pitt *et al.* [21]. However, the approach used, condensing *p*-mentha-2,8-dien-1-ol with 5'-[$^2H_3$]-olivetol, is not suitable for the synthesis of metabolites with a functional group in the 7-position and a modified side-chain. It seems that the use of the terpene synthon in combination with different resorcinol derivatives, labelled or unlabelled, merits attention due to the achieved flexibility, albeit the modest overall yield, where primary and acidic metabolites in the Δ^1-series with an oxidized and/or shortened side-chain can be prepared.

This report is part of a project where unlabelled and isotopically labelled metabolites of Δ^1-THC are to be prepared for further studies of the metabolites and their properties, as well as for use as standards in quantitative measurements.

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REFERENCES

1. Agurell S., Halldin M.M. and Hollister L.E. - In Biochemistry and Physiology of Substance Abuse, Watson R.R. (Ed.), CRC Press, Boca Raton, FL, 1990, p. 137.
2. Halldin M.M., Carlsson S., Kanter S.L., Widman M. and Agurell S. - Arzneim.-Forsch./Drug Res. 32:764 (1982).
3. Cook E. - Alcohol, Drugs, and Driving 2:79 (1986).
4. Mechoulam R., McCallum N.K. and Burstein S. - Chem. Rev. 76:75 (1976).
5. Razdan R.K. - In The Total Synthesis of Natural Products, ApSimon J. (Ed.), John Wiley & Sons, New York, 1981, p.185.
6. Tius M.A., Gu X. and Kerr M.A. - J. Chem. Soc., Chem. Commun. 1:62 (1989).
7. Siegel C., Gordon P.M. and Razdan R.K. - J. Org. Chem. 54:5428 (1989).
8. Huffman J.W., Zhang X., Wu M-J., Joyner H.H. and Pennington W.T. - J. Org. Chem. 56:1481 (1991).
9. Uliss D.B., Handrick R., Dalzell H.C. and Razdan R.K. - J. Amer. Chem. Soc. 100:2929 (1978).
10. Corey E.J. and Crouse D. - J. Org. Chem. 33:298 (1968).
11. Ohlsson A., Lindgren J-E., Leander K. and Agurell S. - In Cannabinoid Assays in Humans, NIDA Research Monogr. 7, Willette R. (Ed.), National Institute on Drug Abuse, Rockville, MD, 1976, p. 48.
12. Handrick G.R., Duffley R.P., Lambert G., Murphy J.G. , Dalzell H.C., Howes J.F., Razdan R.K., Martin B.R., Harris L.S. and Dewey W.L. - J. Med. Chem. 25:1447 (1982).
13. Corey E.J., Gilman N.W. and Ganem B.E. - J. Amer. Chem. Soc. 90:5616 (1968).
14. Pitt C.G., Fowler M.S., Sathe S., Srivastava S.C. and Williams D.L. - J. Amer. Chem. Soc. 97:3798 (1975).
15. Ho Y-S., Liu R.H., Nichols A.W. and Kumar S.D. - J. Forensc. Sci. 35:123 (1990).
16. Danishefsky S. and Kitahara T. - J. Amer. Chem. Soc. 96:7807 (1974).
17. Nilsson J.L.G., Nilsson I.M. and Agurell S. - Acta Chem. Scand. 23:2209 (1969).
18. Liebman A.A., Malarek D.H., Dorsky A.M and Kaegi H.H. - J. Labelled Comp. 7:242 (1971).

19. Gill E.W., Jones G. - J. Labelled Comp. 8:237 (1972).

20. Agurell S., Gustafsson B., Holmstedt B. Leander K., Lindgren J-E., Nilsson I., Sandberg F. and Åsberg M. - J. Pharm. Pharmac. 25:554 (1973).

21. Pitt C.G., Hobbs D.T., Schran H., Twine C.E., Jr., and Williams D.L. - J. Labelled Comp. 11:551 (1975).

22. Hoellinger H., Nguyen-Hoang-Nam, Decauchereux J-F. and Pichat L. - J. Labelled Comp. and Radiopharm. 13:410 (1977).

23. Harvey D.J. and Paton W.D.M. - Adv. Mass Spectrom. 8:1194 (1980).

24. Banijamali A.R., Abou-Taleb N., Van der Schyf C.J., Charalambous A. and Makriyannis A. - J. Labelled Comp. and Radiopharm. 25:73 (1988).

25. Boeren E.G., Heerma W. and Terlouw J.K. - Org. Mass Spectrom. 11:659 (1976).

26. Timmons M.L., Pitt C.G. and Wall M.E. - Tetrahedron Lett. 3129 (1969).

27. Mechoulam R., Braun P. and Gaoni Y. - J. Amer. Chem. Soc. 94:6159 (1972).

28. Nguyen-Hoang-Nam, Beaucourt J.P., Hoellinger H. and Pichat L. - Bull. Soc. Chim. Fr. 1367 (1974).

29. Banijamali A.R., Charalambous A., Van der Schyf C.J. and Makriyannis A. - J. Labelled Comp. and Radiopharm. 24:1479 (1987).