267. Synthesis of Cannabinoid Model Compounds. Part 2[1]): (3*R*, 4*R*)-$\Delta^{1(6)}$-Tetrahydrocannabinol-5″-oic Acid and 4″(*R*, *S*)-Methyl-(3*R*, 4*R*)-$\Delta^{1(6)}$-Tetrahydrocannabinol-5″-oic Acid

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Summary

Two novel cannabinoid model compounds, (3*R*, 4*R*)-$\Delta^{1(6)}$-tetrahydrocannabinol-5″-oic acid (**22**) and 4″(*R*, *S*)-methyl-(3*R*, 4*R*)-$\Delta^{1(6)}$-tetrahydrocannabinol-5″-oic acid (**23**) were synthesized by acid-catalyzed condensation of (+)-*trans*-*p*-mentha-2,8-dien-1-ol (**1**) with the substituted resorcinols **18** and **19** obtained by a *Wittig* reaction between 3,5-bis(benzyloxy)benzaldehyde (**7**) and methyl 4-bromobutanoate (**10**) or methyl 4-bromo-2(*R*, *S*)-methylbutanoate (**11**) resp. with subsequent hydrogenation. The resulting methyl esters **20** and **21** were hydrolyzed to give acids **22** and **23**.

In the course of our investigation of structure-activity relationships in the cannabinoid series we described the synthesis, properties and biotransformation of the non-psychotropic cannabinoid (3*R*, 4*R*)-$\Delta^{1(7)}$-tetrahydrocannabinol [1] [2]. We now wish to report on the synthesis of two novel cannabinoid model compounds, (3*R*, 4*R*)-$\Delta^{1(6)}$-tetrahydrocannabinol-5″-oic acid (**22**) (=$\Delta^{1(6)}$-THC-5″-oic acid) and 4″(*R*, *S*)-methyl-(3*R*, 4*R*)-$\Delta^{1(6)}$-tetrahydrocannabinol-5″-oic acid (**23**) (=4″-methyl-$\Delta^{1(6)}$-THC-5″-oic acid). Both compounds are derivatives of $\Delta^{1(6)}$-THC (**3**), one of the psychotropic principles of the drug hashish. Being mainly interested in acid **23** where the full aliphatic C_5 side chain of the parent compound is retained, acid **22** was prepared to elaborate the synthesis of **23**. Both methyl esters **20** and **21** and the acids **22** and **23** are now investigated for psychotropic activity after intraventricular injection in the cat[3]).

The general stereospecific pathway to (3*R*,4*R*)-$\Delta^{1(6)}$-THC (**3**) and its derivatives consists according to *Petrzilka et al.* [3] in the acid-catalyzed reaction of (+)-*trans*-

[1]) Part 1: see [1].

[2]) Part of the thesis of I.F.

[3]) In two double blind studies the esters **20** and **21** at doses of 10 and 20 mg resp. (spiked cigarettes, total lung delivery 2 mg **20** and 4 mg **21**) could not be distinguished from placebo.

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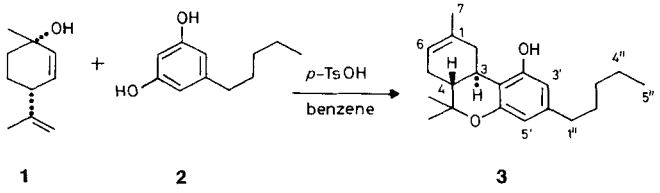
p-mentha-2,8-dien-1-ol (**1**) with properly substituted resorcinols like olivetol (**2**) *(Scheme 1)*. Thus the actual problem in the synthesis of side chain derivatives of $\Delta^{1(6)}$-THC (**3**) lies in the preparation of these resorcinols.

Scheme 1



1 **2** **3**

p-TsOH = *p*-toluenesulfonic acid

Several synthetic routes have been described. *Ohlsson et al.* [4] prepared the resorcinol **18** by a *Wittig* reaction from 3,5-bis(benzyloxy)benzaldehyde (**7**) and methyl 4-bromo-2-butenoate as an intermediate in the synthesis of 5″-hydroxy-$\Delta^{1(6)}$-THC. A similar resorcinol, ethyl 5-(3′,5′-dihydroxyphenyl)pentanoate was used by *Lotz et al.* [5] for the formation of side chain *N*-substituted $\Delta^{1(6)}$-THC's. This compound was prepared by a *Wittig* reaction from 3,5-bis(benzyloxy)benzaldehyde (**7**) and ethyl 4-iodobutanoate. A different approach was chosen by *Crombie et al.* [6] who synthesized the resorcinol **18** from 3,5-dimethoxybenzaldehyde and diethyl ethylidenemalonate.

Our synthesis of acids **22** and **23** was achieved in two parts, first the synthesis of the resorcinols **18** and **19** *(Scheme 2)* which followed a path similar to the one investigated by *Lotz et al.* [5] and second the condensation of **18** and **19** with (+)-*trans*-*p*-mentha-2,8-dien-1-ol (**1**) according to *Petrzilka et al.* [3] *(Scheme 3)* leading to the methyl esters **20** and **21** with the correct configuration at C(3) and C(4) followed by hydrolysis to give the free acids **22** and **23**[4]).

Resorcinols **18** and **19** were synthesized from 3,5-bis(benzyloxy)benzaldehyde (**7**) and the triphenylphosphonium salts **12** and **13** using the *Wittig* condensation as the key reaction. The benzyl group was chosen as protecting group because it could be removed by catalytic hydrogenation simultaneously with the reduction of the double bond of the *Wittig* adducts **16** and **17**.

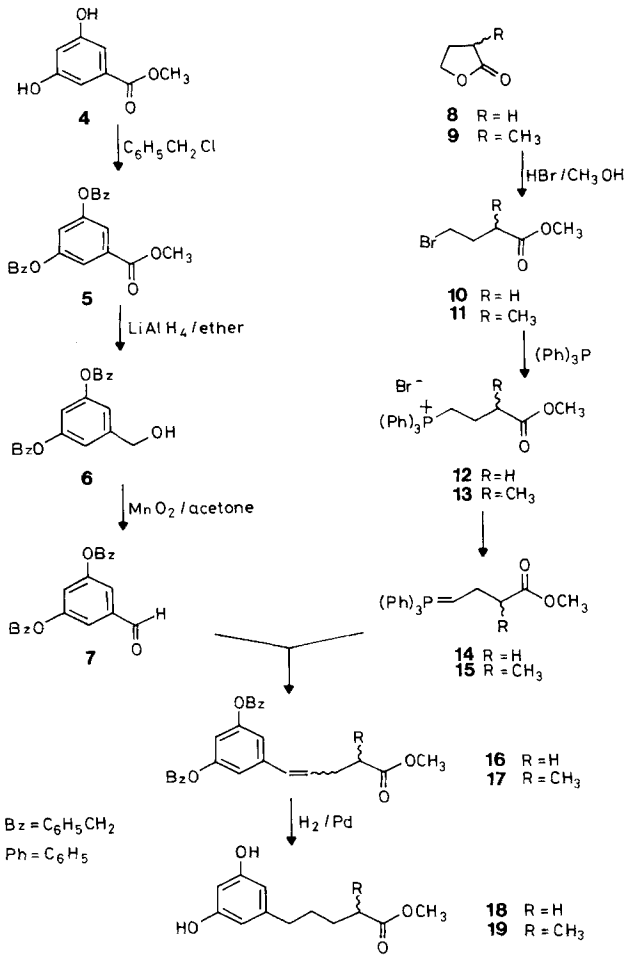
Commercially available methyl 3,5-dihydroxybenzoate (**4**) was reacted with benzyl chloride to give methyl 3,5-bis(benzyloxy)benzoate (**5**) in 79% yield. Reduction of **5** with $LiAlH_4$ in ether led to 3,5-bis(benzyloxy)benzyl alcohol (**6**) in almost quantitative yield (97%). Whereas oxidation of **6** with HNO_3 in dimethylformamide according to *Lotz et al.* [5] gave low yields of 3,5-bis(benzyloxy)benzaldehyde (**7**) (24%) by oxidation with MnO_2 in acetone the yield could be improved (81%).

The second component for the *Wittig* reaction, methyl 4-bromobutanoate (**10**) and methyl 4-bromo-2(*R,S*)-methylbutanoate (**11**) were prepared in 90 and 80% yields resp. from commercially available 4-butyrolactone (**8**) and 2(*R,S*)-methyl-4-butyrolactone (**9**) following *Jones & Wood* [7] [8] by reacting the lactones with dry HBr in absolute methanol. The bromides **10** and **11** were heated with triphenylphosphine yielding the resp. phosphonium salts **12** (89%) and **13** (91%). Phosphonium salt **12** was a crystalline solid while compound **13** resulted as a hygroscopic resin that was dried in dimethylformamide over molecular sieve 0.3 nm to be used for the *Wittig* reaction.

In contrast to *Lotz et al.* [5] who synthesized ethyl 5-[3′,5′-bis(benzyloxy)-phenyl]-4-pentenoate in 22% yield from aldehyde **7** and the triphenylphosphonium salt of ethyl 4-iodobutanoate using tetrahydrofurane as solvent and potassium 2-methyl-2-propanolate as base for the *Wittig* reaction we employed hexamethyl-

[4]) All compounds were checked for purity by gas chromatography (GC.) and thin layer chromatography (TLC.). The structures are in accord with the spectroscopical data (NMR., MS.).

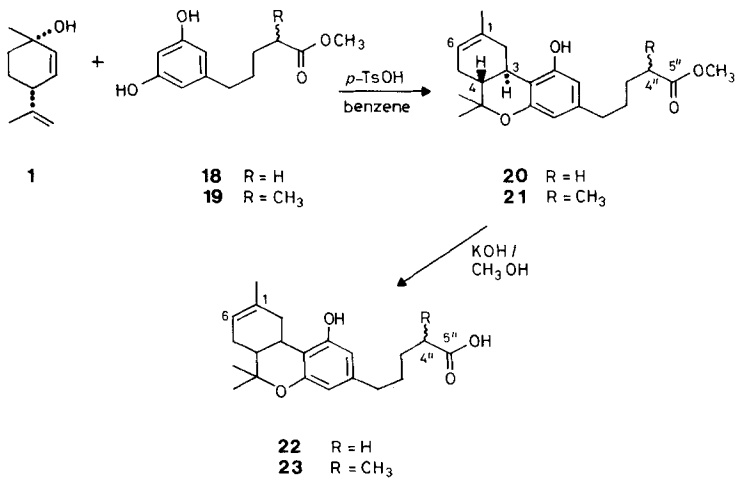
Scheme 2



phosphoric triamide and potassium 2-methyl-2-butanolate thus increasing the yield of **16** to 55%. Under similar conditions methyl 5-[3′,5′-bis(benzyloxy)phenyl-2 (*R, S*)-methyl-4-pentenoate (**17**) could only be obtained in 15% yield. According to GC., NMR. and MS., compounds **16** and **17** consisted of mixtures of the *cis* and *trans* isomers. Since upon hydrogenation single compounds were obtained, no attempt was made to separate the isomers. In both *Wittig* reactions 3,5-bis(benzyloxy)-styrene was found as a major by-product, probably arising from an attack of the base at H–C(2) of the phosphonium salts **12** and **13** with subsequent fragmentation of the molecule leading to methylidene triphenylphosphorane. Attempts to raise the yield of **17** by changing the conditions of the reaction failed.

The resorcinols methyl 5-(3′,5′-dihydroxyphenyl)pentanoate (**18**) (87%) and methyl 5-(3′,5′-dihydroxyphenyl)-2 (*R, S*)-methylpentanoate (**19**) (96%) were obtained easily from **16** and **17** resp. by catalytic hydrogenation over Pd/C.

Scheme 3



The resorcinols **18** and **19** were reacted with (+)-*trans-p*-mentha-2,8-dien-1-ol (**1**) as described by *Petrzilka et al.* [3] to give methyl $\Delta^{1(6)}$-THC-5″-oate (**20**) and methyl 4″-methyl-$\Delta^{1(6)}$-THC-5″-oate (**21**) resp. in yields of 48 and 44%. Both esters **20** and **21** were hydrolyzed with methanolic KOH-solution to give the free acids **22** (94%) and **23** (92%). The NMR. spectra of ester **20** and acid **22** *(Fig. 1)* and ester **21** and acid **23** *(Fig. 2)* as well as the MS. of these compounds are in agreement with the proposed structures. Calculated on methyl 3,5-dihydroxybenzoate (**4**) acid **22** was obtained in an over all yield of 13.4%, acid **23** in 3.6% yield.

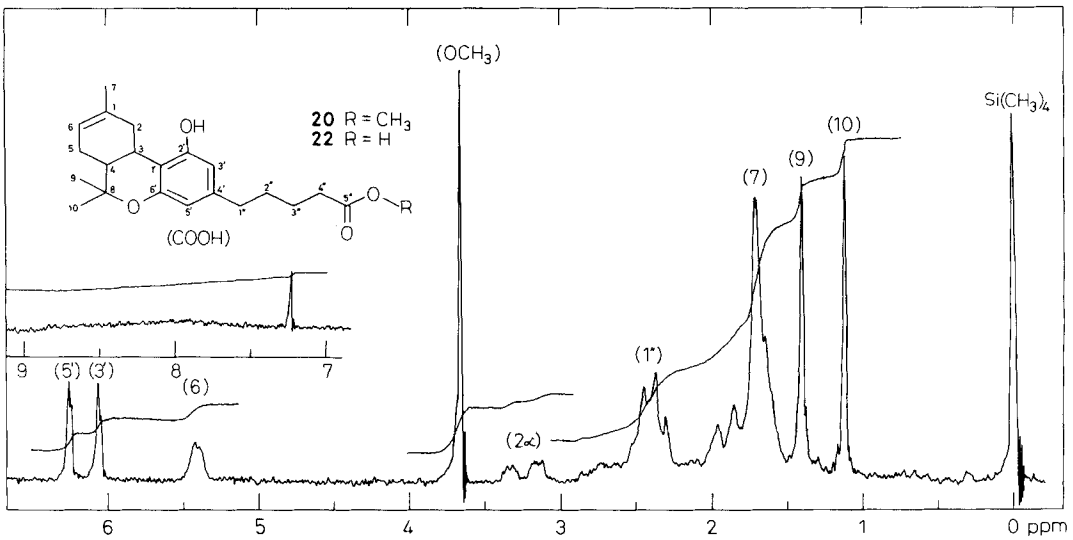


Fig. 1. *90-MHz-^{1}H-NMR. spectra of methyl $\Delta^{1(6)}$-THC-5″-oate* (**20**) *and $\Delta^{1(6)}$-THC-5″-oic acid* (**22**) *in $CDCl_3$.* Peak at $\delta = 3.7$ ppm only in **20**, peak at $\delta = 7.5$–8.5 ppm only in **22**.

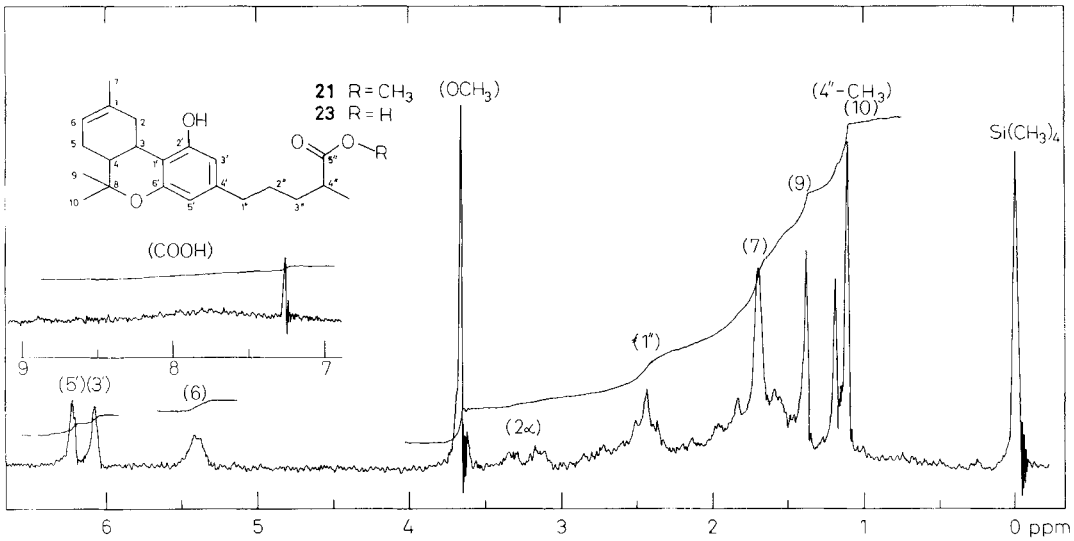


Fig. 2. *90-MHz-^{1}H-NMR. spectra of methyl 4''(R,S)-methyl-$\Delta^{1(6)}$-THC-5''-oate* (**21**) *and 4'' (R,S)-methyl-$\Delta^{1(6)}$-THC-5''-oic acid* (**23**) *in $CDCl_3$.* Peak at $\delta = 3.7$ ppm only in **21**, peak at $\delta = 7.5$–8.5 ppm only in **23**.

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Experimental Part

General remarks. Preparative chromatography was carried out on silica gel (*Merck*, 0.063–0.2 mm), thin layer chromatography (TLC.) on precoated plates, silica gel 60 F 254 *(Merck)*. Gas chromatograms were performed on a *Hewlett-Packard* 5711-A gas chromatograph (FID.) on columns (1.80 m × 2 mm) of 3% SE-30 or 3% OV-17 on Gaschrom Q. Melting points (m.p.) are not corrected. 90-MHz-^{1}H-NMR. spectra: in $CDCl_3$ unless otherwise stated, chemical shifts in δ rel. to tetramethylsilane. MS. (70 eV): *m/z* (relative intensity in %, structure of fragment ions).

1. Preparation of methyl 5-(3',5'-dihydroxyphenyl)pentanoate (18) and methyl 5-(3',5'-dihydroxyphenyl)-2(*R, S*)-methylpentanoate (19) *(Scheme 2).* – 1.1. *Methyl 3,5-bis(benzyloxy)benzoate* (**5**) *from methyl 3,5-dihydroxybenzoate* (**4**). A mixture of 84.5 g **4** *(EGA-Chemie)* (0.5 mol), 127 ml benzyl chloride (1.1 mol) and 76.0 g dry K_2CO_3 in 50 ml abs. acetone was heated under reflux for 48 h. The acetone was removed *in vacuo* and the residue partitioned between ether/H_2O. From the ether phase 198 g oil were obtained that were crystallized from 100 ml methanol. Yield: 137.5 g (79%), m.p. 68–70°. – ^{1}H-NMR.: 3.85 (*s*, 3 H, OCH_3); 5.01 (*s*, 4 H, benzylic H); 6.77 (*t*, $J = 2$, 1 H, H–C(4)); 7.36 (*m*, 12 H). – MS.: 348 (18, M^+); 317 (2, $M^+ - OCH_3$); 181 (7, $M^+ - C_6H_5CH_2OH - COOCH_3$); 91 (100); 65 (14).

1.2. *3,5-Bis(benzyloxy)benzylalcohol* (**6**) *from* **5**. To a stirred suspension of 10.0 g (0.26 mol) $LiAlH_4$ in 200 ml abs. ether were added dropwise a solution of 69.6 g (0.2 mol) of **5** in 1 l abs. ether and the mixture was refluxed for 1 h. After cooling 40 ml NaOH (1 M) were added, the mixture was refluxed for another h, the precipitate filtered off, washed with ether and the ether removed *in vacuo*. The crude product (62.4 g, 97.5%) was crystallized from methanol to give **6**, m.p. 79–81°. – ^{1}H-NMR.: 2.43 (*s*, 1 H, OH); 4.48 (*s*, 2 H, CH_2OH); 4.93 (*s*, 4 H, benzylic H); 6.53 (*m*, 3 H, H–C(2,4,6)); 7.3 (*m*, 10 H). – MS.: 320 (17, M^+); 289 (2, $M^+ - CH_2OH$); 181 (14, $M^+ - C_6H_5CH_2OH - CH_2OH$); 91 (100); 65 (2).

1.3. *3,5-Bis(benzyloxy)benzaldehyde* (**7**) *from* **6**. To a stirred solution of 32.0 g (0.1 mol) **6** in 500 ml dry acetone at 0° were added 160 g MnO_2. The mixture was kept at 23° for 1 h, the MnO_2 filtered off and the acetone removed *in vacuo*. The residue was crystallized from methanol to give 25.8 g (81%) **7**, m.p. 78–80°. – ^{1}H-NMR.: 4.99 (*s*, 4 H, benzylic H); 6.80 (*t*, $J=2$, 1 H, H–C(4)); 7.04 (*d*, $J=2$, 2 H, H–C(2,6)); 7.33 (*m*, 10 H); 9.80 (*s*, 1 H, CHO) – MS.: 318 (48, M^+); 227 (6, $M^+ - C_7H_7$); 181 (27, $M^+ - C_6H_5CH_2OH - COH$); 91 (100).

1.4.1. *Methyl 4-bromobutanoate* (**10**) *from 4-butyrolactone* (**8**). Dry HBr (40 g, 0.5 mol) was introduced at 0° to a solution of 16.2 ml (0.2 mol) **8** *(Sigma)* in 50 ml abs. methanol. The solution was kept at 23° for 48 h, poured on ice and extracted with H_2O. After washing with 10% $NaHCO_3$-solution the ether was removed *in vacuo* at 20°. Yield: 32.5 g (90%) **10** (oil). – ^{1}H-NMR.: 2.0–2.6 (*m*, 4 H, H–C(2), H–C(3)); 3.46 (*t*, $J=6$, 2 H, H–C(4)); 3.70 (*s*, 3 H, OCH_3). – MS.: 149/151 (21, $M^+ - OCH_3$); 121/123 (9, $M^+ - COOH_3$); 107/109 (2, $M^+ - CH_2COOH_3$); 101 (28, M^+-Br); 93/95 (2, $M^+ - CH_2CH_2COOH_3$); 74 (100, $M^+ - CH_2 = CHBr$); 59 (33, $COCH_3^+$).

1.4.2. *Methyl 4-bromo-2(*R,S*)-methylbutanoate* (**11**) *from 2(*R,S*)-methyl-4-butyrolactone* (**9**). Compound **9** (20.0 g, 0.2 mol; *Aldrich-Europe*) was reacted as described under 1.4.1 yield: 31.2 g (80%) after destillation, b.p. 76°/15 Torr. – ^{1}H-NMR.: 1.18 (*d*, $J=7$, 3 H, H_3C–C(2)); 1.7–2.5 (*m*, 2 H, 2 H–C(3)); 2.5–2.9 (*m*, 1 H, H–C(2)); 3.4 (*t*, $J=7$, 2 H, 2 H–C(4)); 3.70 (*s*, 3 H, OCH_3). – MS.: 163/165 (6, $M^+ - OCH_3$); 135/137 (8, $M^+ - COOCH_3$); 115 (4, M^+-Br); 107/109 (3, $M^+ - CHCH_3COOCH_3$); 88 (100, $M^+ - CH_2 = CHBr$).

1.5.1. *Triphenylphosphonium salt* **12** *from* **10**. A mixture of 18.1 g (0.1 mol) **10** and 26.2 g (0.1 mol) triphenylphosphine in 100 ml toluene was heated under reflux for 48 h. The crystalline product was filtered off and washed with toluene. Yield: 39.4 g (89%). – ^{1}H-NMR. ($(CD_3)_2S=O$): 1.8 (*m*, 2 H, 2 H–C(3)); 2.69 (*t*, $J=6.5$, 2 H, 2 H–C(2)); 3.60 (*s*, 3 H, OCH_3); 3.8 (*m*, 2 H, 2 H–C(4)); 7.9 (*m*, 15 H).

1.5.2. *Triphenylphosphonium salt* **13** *from* **11**. Compound **11** (9.75 g, 0.05 mol) was reacted as under 1.5.1. The resinous product **13** was washed with toluene several times and dried at 0.01 Torr. Yield: 21.0 g (92%). – ^{1}H-NMR.: 1.3 (*d*, $J=7$, 3 H, H_3C–C(2)); 1.6–2.2 (*m*, 2 H, 2 H–C(3)); 3.0–3.6 (*m*, 2 H, 2 H–C(4)); 3.70 (*s*, 3 H, OCH_3); 3.8–4.5 (*m*, 1 H, H–C(2)); 7.8 (*m*, 15 H).

1.6.1. *Methyl 5-[3',5'-bis(benzyloxy)phenyl]-4-pentenoate* (**16**) *from* **7** *and* **12**. Potassium (465 mg, 16.5 mmol) was reacted with dry 2-methyl-2-butanol (30 ml) under argon. The excess alcohol was destilled of and the potassium 2-methyl-2-butanolate was dissolved in 80 ml hexamethylphosphoric triamide. At 0° **12** (6.65 g, 15 mmol) was added with simultaneous formation of the orange coloured ylide **14**. After 15 min a solution of 4.77 g (15 mmol) **7** in 60 ml benzene was added, the reaction continued at 20° for 1 h and the reaction mixture partitioned between ether/H_2O. The organic phase yielded 9.5 g of an oil that was chromatographed on silica gel (400 g, fract. size 400 ml, eluent: fract. 1–50 benzene/petroleum ether 40–60° 1:1, from fract. 51 benzene/petroleum ether 3:1). Fractions 52–72 contained 3.33 g (55%) chromatographically pure **16**. – ^{1}H-NMR.: 2.5 (*m*, 4 H, 2 H–C(2), 2 H–C(3)); 3.7 (*s*, 3 H, OCH_3); 5.05 (*s*, 4 H, benzylic H); 5.6 (*m*, 1 H, H–C(4)); 6.4 (*m*, 1 H, H–C(5)); 6.5 (*s*, 3 H, H–C(2',4',6')); 7.4 (*m*, 10 H). – MS.: 402 (11, M^+); 371 (1, $M^+ - OCH_3$); 181 (12, $M^+ - C_6H_5CH_2OH - CH = CHCH_2CH_2COOCH_3$); 91 (100); 65 (6).

1.6.2. *Methyl 5-[3',5'-bis(benzyloxy)phenyl]-2(*R,S*)-methyl-4-pentenoate* (**17**) *from* **7** *and* **13**. Potassium 2-methyl-2-butanolate, prepared as under 1.6.1 from 1.81 g potassium, was dissolved in 150 ml dry dimethylformamide and a solution of 19.2 g (42 mmol) **17** in 150 ml dimethylformamide (dried over molecular sieve 0.3 nm for 24 h) was added at 0°. After 15 min a solution of 13.4 g (42 mmol) **7** in 150 ml benzene was added to the ylide **15**, the reaction continued at 20° for 1 h and the mixture worked up as above. Fractions 29–55 contained 2.62 g (15%) pure **17**. – ^{1}H-NMR.: 1.2 (*d*, $J=7$, 3 H, H_3C–C(2)); 2.5 (*m*, 3 H, H–C(2), 2 H–C(3)); 3.6 (*s*, 3 H, OCH_3); 5.0 (*s*, 4 H, benzylic H); 5.55 (*m*, 1 H, H–C(4)); 6.4 (*m*, 1 H, H–C(5)); 6.55 (*s*, 3 H, H–C(2',4',6')); 7.4 (*m*, 10 H). – MS.: 416 (65, M^+); 181 (30, $M^+ - C_6H_5CH_2OH - CH = CHCH_2CH(CH_3)COOCH_3$); 91 (100); 65 (11).

1.7.1. *Methyl 5-(3',5'-dihydroxyphenyl)pentanoate* (**18**) *from* **16**. Compound **16** (4.02 g, 10 mmol) was hydrogenated in 100 ml ethyl acetate over 10% Pd/C (1 g). The reaction was monitored by GC. The catalyst was removed by filtration and the solvent evaporated *in vacuo*. The crude product was crystallized from ethyl acetate/CCl_4 to give 1.95 g (87%) **18**, m.p. 63–68°. – ^{1}H-NMR.: 1.62 (*m*, 4 H, 2 H–C(2), 2 H–C(5)); 2.4 (*m*, 4 H, 2 H–C(3), 2 H–C(4)); 3.61 (*s*, 3 H, OCH_3); 6.19 (*s*, 3 H, H–C(2',4',6')); 8.05 (*s*, 2 H, 2 OH). – MS.: 224 (29, M^+); 193 (12, $M^+ - OCH_3$); 165 (3, $M^+ - COOCH_3$); 151 (3, $M^+ - CH_2COOCH_3$); 137 (31, $M^+ - CH_2CH_2COOCH_3$); 124 (100, $M^+ - CH_2 = CHCH_2COOCH_3$); 123 (29, $M^+ - CH_2CH_2CH_2COOCH_3$).

1.7.2. *Methyl 5-(3',5'-dihydroxyphenyl)-2(*R,S*)-methylpentanoate* (**19**) *from* **17**. Compound **17** (2.09 g) was hydrogenated as under 1.7.1 yield: 1.15 g (96%) as oil. – ^{1}H-NMR.: 1.12 (*d*, $J = 6$, 3 H, $H_3C-C(2)$); 1.6 (*m*, 4 H, 2 H–C(3), 2 H–C(4)); 2.5 (*m*, 3 H, 1 H–C(2), 2 H–C(5)); 3.62 (*s*, 3 H, OCH_3); 6.19 (*s*, 3 H, H–C(2',4',6')); 7.96 (*s*, 2 H, 2 OH). – MS.: 238 (34, M^+); 207 (8, $M^+ - OCH_3$); 179 (6, $M^+ - COOCH_3$); 151 (7, $M^+ - CH(CH_3)COOCH_3$); 137 (25, $M^+ - CH_2CH(CH_3)COOCH_3$); 124 (100, $M^+ - CH_2{=}CHCH(CH_3)COOCH_3$); 123 (29, $M^+ - CH_2CH_2CH(CH_3)COOCH_3$).

2. Preparation of (3*R*,4*R*)-$\Delta^{1(6)}$-THC-5″-oic acid (22) and 4″(*R*,*S*)-methyl-(3*R*,4*R*)-$\Delta^{1(6)}$-THC-5″-oic acid (23) *(Scheme 3).* – 2.1.1. *Methyl $\Delta^{1(6)}$-THC-5″-oate* (**20**) *from* **1** *and* **18**. A mixture of 1.90 g (8.5 mmol) **18**, 1.29 g **1** *(Firmenich, Genf)* and 325 mg *p*-toluenesulfonic acid · H_2O in 170 ml dry benzene was refluxed for 2 h and partitioned between 10% $NaHCO_3$-solution and ether. The organic phase yielded 3.36 g crude product that was chromatographed on 200 g silica gel (fract. size 200 ml, eluent: petroleum ether 40–60°/ether 85:15). Fractions 14–20 contained 1.46 g (48%) pure **20**. – ^{1}H-NMR.: see *Figure 1*. – MS.: 358 (80, M^+); 343 (9, $M^+ - CH_3$); 327 (12, $M^+ - OCH_3$); 315 (14, $M^+ - C_3H_7$); 290 (16, $M^+ - 68$); 275 (76, $M^+ - 68 - CH_3$); 258 (19, $M^+ - CH_2{=}CHCH_2COOCH_3$); 243 (5, $M^+ - CH_2{=}CHCH_2COOCH_3 - CH_3$).

2.1.2. *Methyl 4″*(R,S)*-methyl-$\Delta^{1(6)}$-THC-5″-oate* (**21**) *from* **1** *and* **19**. **21** was prepared from 1.07 g (4.5 mmol) **19** and purified as under 2.1.1 yield: 740 mg (44%). – ^{1}H-NMR.: see *Figure 2*. – MS.: 372 (100, M^+); 357 (16, $M^+ - CH_3$); 341 (15, $M^+ - OCH_3$); 329 (19, $M^+ - C_3H_7$); 304 (17, $M^+ - 68$); 289 (93, $M^+ - 68 - CH_3$); 258 (37, $M^+ - CH_2{=}CHCH(CH_3)COOCH_3$).

2.2.1. *$\Delta^{1(6)}$-THC-5″-oic acid* (**22**) *from* **20**. A mixture of 1.25 g (3.5 mmol) **20**, 20 ml methanol and 5 ml KOH 10M was heated under reflux for 30 min, poured on ice and extracted with ether. The aqueous phase was acidified (conc. hydrochloric acid, pH 1) and extracted (ether). The organic phase yielded 1.13 g (94%) **22**. – ^{1}H-NMR.: see *Figure 1*. – MS.: 344 (85, M^+); 329 (11, $M^+ - CH_3$); 301 (19, $M^+ - C_3H_7$); 299 (6, $M^+ - COOH$); 276 (21, $M^+ - 68$); 261 (100, $M^+ - 68 - CH_3$); 258 (16, $M^+ - CH_2{=}CHCH_2COOH$); 243 (4, $M^+ - CH_2{=}CHCH_2COOH - CH_3$).

2.2.2. *4″(*R,S*)-Methyl-$\Delta^{1(6)}$-THC-5″-oic acid* (**23**) *from* **21**. Compound **21** (372 mg) was saponified as under 2.2.1 yield 329 mg (92%) **23**. – ^{1}H-NMR.: see *Figure 2*. – MS.: 358 (78, M^+); 343 (10, $M^+ - CH_3$); 315 (16, $M^+ - C_3H_7$); 290 (21, $M^+ - 68$); 275 (100, $M^+ - 68 - CH_3$); 258 (24, $M^+ - CH_2{=}CHCH(CH_3)COOH$).

REFERENCES

[1] *M. Binder, H. Edery & G. Porath,* in G. Nahas & W.D.M. Paton (Ed.), 'Marihuana: Biological Effects', Pergamon Press, Oxford 1979, p. 71.

[2] *M. Binder & U. Barlage,* Helv. *63*, 255 (1980).

[3] *T. Petrzilka, W. Haefliger & C. Sikemeier,* Helv. *52*, 1102 (1969).

[4] *A. Ohlsson, S. Agurell, K. Leander, J. Dahmen, H. Edery, G. Porath, S. Levy & R. Mechoulam,* Acta Pharm. Suec. *16*, 21 (1979).

[5] *F. Lotz, U. Kraatz & F. Korte,* Liebigs Ann. Chem. *1977*, 1132.

[6] *L. Crombie, W.M.L. Crombie & G.W. Kilbee,* Tetrahedron Lett. *49*, 4773 (1979).

[7] *G. Jones & J. Wood,* Tetrahedron *21*, 2529 (1965).

[8] *G. Jones & J. Wood,* Tetrahedron *21*, 2961 (1965).