

256. Synthesis of Cannabinoid Model Compounds

Part 3¹⁾

**(6a*R*, 10a*R*)-*N*-Ethyl- Δ^8 -tetrahydrocannabinol-18-amide,
(6a*R*, 10a*R*, 17*RS*)-*N*-Ethyl-17-methyl- Δ^8 -tetrahydrocannabinol-18-amide
and (6a*R*, 10a*R*)-17,18-Didehydro- Δ^8 -tetrahydrocannabinol**

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Dedicated to Prof. Dr. Ch. Tamm on the occasion of his 60th birthday

(1. IX. 83)

Summary

The novel cannabinoids (6a*R*, 10a*R*)-*N*-ethyl- Δ^8 -tetrahydrocannabinol-18-amide (**15**) and (6a*R*, 10a*R*, 17*RS*)-*N*-ethyl-17-methyl- Δ^8 -tetrahydrocannabinol-18-amide (**16**), designed as cannabinoid affinity ligands, were synthesized from the corresponding acids **11** and **12** via the *N*-hydroxysuccinimide esters. Amide **16** was tested in the rat and was generalized to Δ^9 -tetrahydrocannabinol, being 5 times less potent than the training drug. An improved synthesis of (6a*R*, 10a*R*)-17,18-didehydro- Δ^8 -tetrahydrocannabinol (**23**) is reported. As model reaction for the preparation of a tritiated Δ^8 -tetrahydrocannabinol, compound **23** was selectively deuterated at C(17) and C(18) in benzene/Et₃N using [(C₆H₅)₃P]₃RuCl₂ as catalyst.

Recently, we have reported the synthesis of (6a*R*, 10a*R*)- Δ^8 -tetrahydrocannabinol-18-oic acid²⁾ (= Δ^8 -THC-18-oic acid; **11**) and (17*RS*)-17-methyl- Δ^8 -THC-18-oic acid (**12**) [1]. The latter compound was designed as an affinity ligand to isolate Δ^9 (or Δ^8)-THC-binding macromolecules (the 'THC receptor' [2]) from neuronal membrane fractions. Acid **12** retains the full structure of Δ^9 -THC and was to be coupled to BrCN-activated *Sepharose* via an ethylamino spacer. The closest model to the moiety attached to the *Sepharose* is the *N*-ethyl amide of acid **12**. To evaluate efficient techniques for coupling the acid **12** to the aminoethyl-*Sepharose* and to study whether the amide retains psychotropic activity, i.e. binds to the THC receptor, the *N*-ethyl amides **15** and **16** of acids **11** and **12**, respectively, were synthesized.

¹⁾ Part 2: see [1].

²⁾ This numbering of the cannabinoid skeleton is based on a suggestion by Schoenfeld [3]. It is semisystematic. The numbering of the ring system follows the IUPAC rule but the substituents are numbered consecutively.

1. *Syntheses of Amides 15 and 16 (Scheme 1).* – Basically, the acids **11** and **12** were obtained as described in [1] ($1 + 2 \rightarrow 4 \rightarrow 6(+8) \rightarrow 9 \rightarrow 11$; $1 + 3 \rightarrow 5 \rightarrow 7(+8) \rightarrow 10 \rightarrow 12$). However, the yield of Wittig adduct **5** was increased to 37% by substituting the phosphonium bromide [1] by the corresponding iodide **3**. Since both amides and acids were intended as model compounds for the affinity gels we restricted ourselves in transforming **11** and **12** into **15** and **16**, respectively, to conditions that would allow the coupling of the acids to the activated *Sepharose* as well. The THC molecule is very reactive, especially involvement of the free phenolic OH group has to be avoided. The use of 1-ethyl-3-[3'-(dimethylamino)propyl]carbodiimide for the amide formation proved highly unsatisfactory; both amides **15** and **16** were obtained in yields of 7%. Following the method of Cook [4], **15** and **16** were obtained in 70% yield by reacting **11** and **12**, respectively, with *N*-hydroxysuccinimide in anhydrous MeCN in the presence of dicyclohexylcarbodiimide (DCC) and treating the intermediate esters **13** and **14**, respectively, with EtNH₂ in aqueous dioxane.

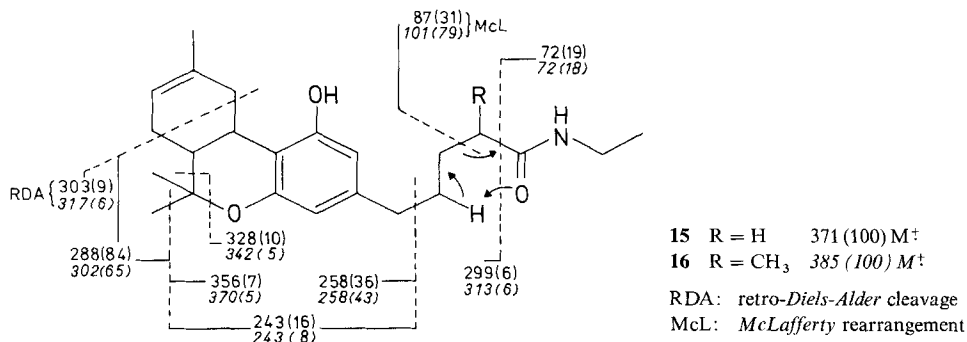


Fig. 1. Fragments (m/z) in the MS of the Amides **15** and **16**. Values of **16** in italics, relative intensities in parentheses.

Amide **16** was tested for psychotropic activity in the rat [5]. In a drug-discrimination paradigm the compound was generalized to Δ^9 -THC at 5 times the concentration of the training drug. This proves that the model compound retains affinity to the postulated THC receptor and justifies our choice of acid **12** as affinity ligand. Metabolic transformation, pharmacokinetics and triglyceride/phospholipid partitioning of amide **16** are investigated at present and will be reported elsewhere.

The structures of the amides **15** and **16** were proven by their mass spectra and ¹H-NMR spectra. The MS are given in Fig. 1. In addition to the known fragmentations of the isoprenoid part of the molecule [6] [7], prominent fragment ions arise from cleavage of the substituted pentyl side chain. Decoupling allowed to localize all signals of the 250-MHz NMR spectrum of **16** (Fig. 2).

Since the ¹H-NMR spectra of tetrahydrocannabinols have been analyzed in detail [8] only signals relevant to the substituted side chain will be discussed here. The CH₃CH₂NHCO-function gives rise to a *dq* (CH₃CH₂) centered at 3.28 and 3.25, a *t* at 5.58 (NH), and a *t* at 1.1 ppm (CH₃CH₂). The protons at C(15) were located as a *quint* (*J*_{14,15} = *J*_{15,16} = 7 Hz) at 1.54 ppm by irradiation at 2.42 ppm, the position of the signals of H-C(14). Irradiation at 1.54 ppm revealed the location of the 2H-C(16) at 1.41 ppm. The CH₃-C(17) leads to a *d* at 1.1 ppm. By decoupling at this position, H-C(17) was located at 2.14 ppm.

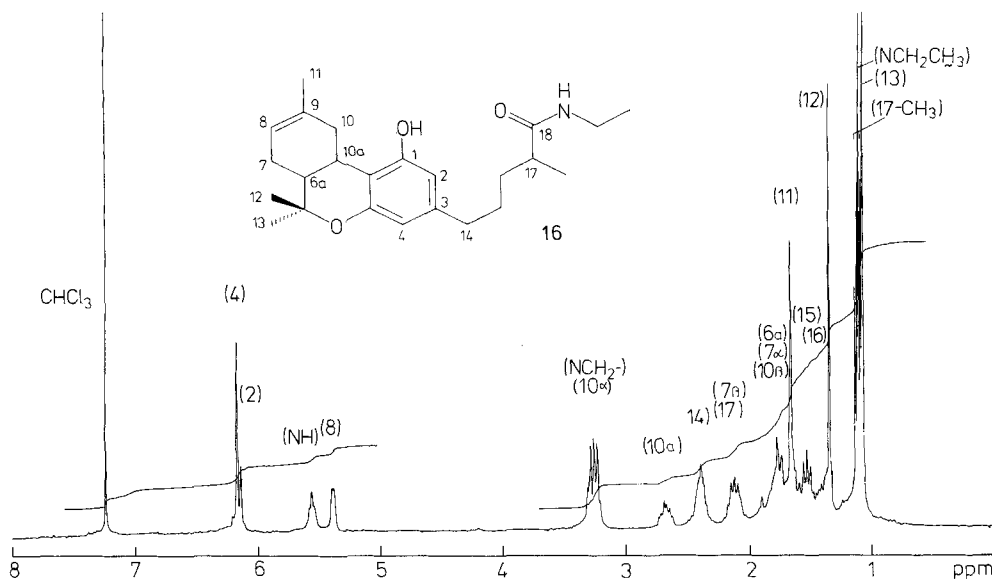
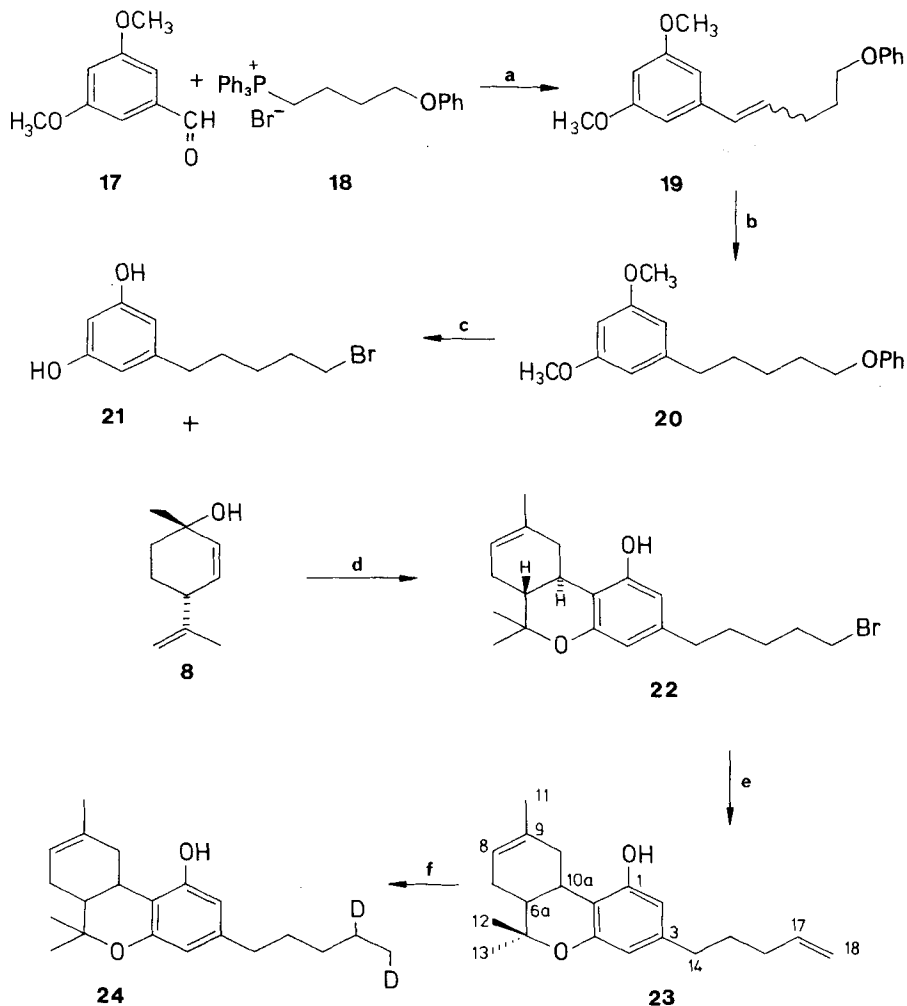


Fig. 2. 250-MHz ^1H -NMR Spectrum of (6aR, 10aR, 17RS)-N-Ethyl-17-methyl- Δ^8 -tetrahydrocannabinol-18-amide (**16**) in CDCl_3

2. *Synthesis of 17,18-Didehydro- Δ^8 -THC (23) and [17,18- $^2\text{H}_2$]- Δ^8 -THC (24) (Scheme 2).* – Essentially following the procedure of Pitt *et al.* [9], several changes were introduced. The 3,5-dimethoxybenzaldehyde (**17**) was reacted with the triphenylphosphonium bromide **18** in Et_2O in the presence of BuLi to give a *cis/trans*-mixture of the Wittig adduct **19** (62%). This reaction did not work at the concentrations given in [9] but proceeded smoothly at 10fold dilution. Catalytic hydrogenation of **19** (Pd/C, EtOH) gave **20** in 95% yield. Using BBr_3 in benzene, **20** was transformed into 5-(5-bromopentyl)resorcinol (**21**; 80%). Condensation of **21** with (+)-*trans-p*-mentha-2,8-dien-1-ol (**8**) yielded (6aR, 10aR)-18-bromo- Δ^8 -THC (**22**; 38%). In contrast to Pitt *et al.* [9] we succeeded in isolating 17,18-didehydro- Δ^8 -THC (**23**) in 14% yield from the mixture of products resulting from the dehydrohalogenation of **22** with potassium 3-ethylpentan-3-olate in benzene/toluene. The synthesis of 17,18-didehydro- Δ^9 -THC described by Pitt *et al.* [9] by adding HCl to the 8,9-double bond of **23** followed by dehydrohalogenation could not be reproduced in our laboratory. Finally, 17,18-didehydro- Δ^8 -THC (**23**) was deuterated selectively in benzene/ Et_3N in the presence of $[(\text{C}_6\text{H}_5)_3\text{P}]_3\text{RuCl}_2$ to give [17,18- $^2\text{H}_2$]- Δ^8 -THC (**24**) in 49% yield. The essential advantage of this synthesis becomes evident: by introducing the radioactive isotope ^3H in the last reaction, extensive handling of radiolabelled compounds can be avoided. The structures of all synthetic intermediates were established by MS and ^1H -NMR spectroscopy.

The MS of 17,18-didehydro- Δ^8 -THC (**23**; M^+ at m/z 312) closely resembles the one of Δ^8 -THC except for the base peak which arises from the cleavage between C(14) and C(15) including a *McLafferty* rearrangement (m/z 258; $M^+ - \text{C}_4\text{H}_6$). The MS of the deuterated derivative **24** revealed 15.6% non-, 27.3% mono-, 32.4% bi-, 15.3% tri-, 6.3%

Scheme 2

**a** BuLi/Et₂O**b** H₂/Pd/C, EtOH**c** BBr₃/benzene**d** TsOH/benzene**e** Et₃CO⁻K⁺/toluene, benzene**f** D₂/[(C₆H₅)₃P]₃RuCl₂, Et₃N/benzene

tetra- and 2.1% pentadeuteration, giving a total of 1.73 ²H per molecule. The ¹H-NMR spectrum (Fig. 3) of **23** reveals 3 additional signals of olefinic protons between 4.8 and 6.0 ppm arising from H-C(17) and H-C(18) while the usual *t* of H-C(18) of Δ⁸-THC at 0.9 ppm is lacking. Broad signals at 0.85 and 1.29 ppm in the 250-MHz ²H-NMR spectrum of **24** indicate the presence of deuterium atoms mostly at C(18) and C(16/17).

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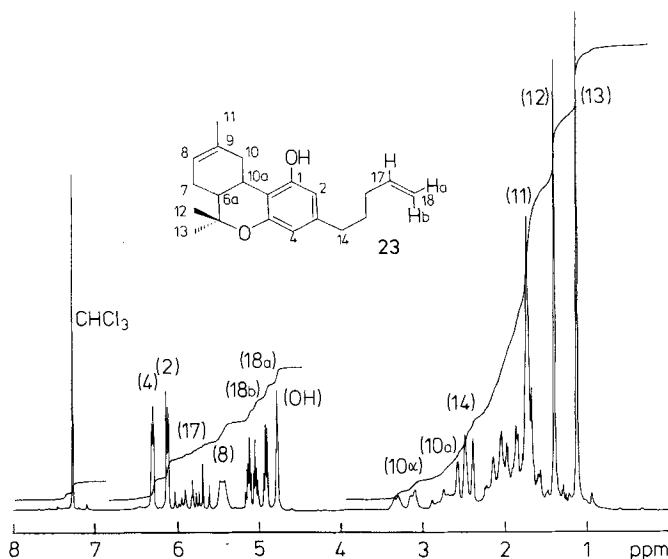


Fig. 3. 80-MHz ^1H -NMR Spectrum of 17, 18-Didehydro- Δ^8 -THC (**23**) in CDCl_3

Experimental Part

General Remarks. See [1].

1. (6*a*R, 10*a*R)-*N*-Ethyl- Δ^8 -tetrahydrocannabinol-18-amide (= *N*-Ethyl-5-[(6*a*R, 10*a*R)-1-hydroxy-6,6,9-trimethyl-6*a*,7,10,10*a*-tetrahydro-6*H*-dibenzo[*b,d*]pyran-3-yl]pentanamide; **15**) and (6*a*R, 10*a*R, 17*RS*)-*N*-Ethyl-17-methyl- Δ^8 -tetrahydrocannabinol-18-amide (= (2*RS*)-*N*-Ethyl-5-[(6*a*R, 10*a*R)-1-hydroxy-6,6,9-trimethyl-6*a*,7,10,10*a*-tetrahydro-6*H*-dibenzo[*b,d*]pyran-3-yl]-2-methylpentanamide; **16**). Only procedures that are not identical to those already published [1] are given in detail.

1.1. (6*a*R, 10*a*R)- Δ^8 -Tetrahydrocannabinol-18-oic Acid (= 5-[(6*a*R, 10*a*R)-1-Hydroxy-6,6,9-trimethyl-6*a*,7,10,10*a*-tetrahydro-6*H*-dibenzo[*b,d*]pyran-3-yl]pentanoic Acid; **11**). See [1].

1.2. (6*a*R, 10*a*R, 17*RS*)-17-Methyl- Δ^8 -tetrahydrocannabinol-18-oic Acid (= (2*RS*)-5-[(6*a*R, 10*a*R)-1-Hydroxy-6,6,9-trimethyl-6*a*,7,10,10*a*-tetrahydro-6*H*-dibenzo[*b,d*]pyran-3-yl]-2-methylpentanoic Acid; **12**). – 1.2.1. Methyl (2*RS*)-4-Iodo-2-methylbutanoate. A solution of 2.15 g (11 mmol) of methyl (2*RS*)-4-bromo-2-methylbutanoate [1] in 7.5 ml of dry acetone was added dropwise to 2.47 g (16.5 mmol) of NaI in 30 ml of dry acetone, and the mixture was heated under reflux for 90 min. The solvent was removed under N_2 and the residue partitioned between $\text{Et}_2\text{O}/\text{H}_2\text{O}$. The org. phase yielded 2.62 g (98%) of pure methyl 4-iodo-2-methylbutanoate. ^1H -NMR: 1.17 (*d*, $J = 7$, 3H, $\text{CH}_3\text{-C}(2)$); 1.7 (*m*, 2H, $2\text{H-C}(3)$); 2.4–2.8 (*m*, 1H, $\text{H-C}(2)$); 3.20 (*t*, $J = 6$, 2H, $2\text{H-C}(4)$); 3.61 (*s*, 3H, CH_3O). MS: 211 (13, $M^+ - \text{OCH}_3$), 183 (9, $M^+ - \text{COOCH}_3$), 155 (6, $M^+ - \text{CH}(\text{CH}_3)\text{COOCH}_3$), 115 (75, $M^+ - \text{I}$), 88 (16, $\text{CH}_3\text{CH}=\text{C}(\text{OH})\text{OCH}_3^+$), 59 (100, COOCH_3^+).

1.2.2. (3-(Methoxycarbonyl)butyl)triphenylphosphonium Iodide (**3**). A solution of 2.62 g (10.8 mmol) of methyl (2*RS*)-4-iodo-2-methylbutanoate and 2.27 g (8.65 mmol) of Ph_3P in 20 ml of dry benzene was heated under reflux for 65 h. The resinous **3** was allowed to separate, washed $5 \times$ with benzene (30 ml) and dried at 0.01 Torr: 4.27 g (98%). ^1H -NMR (D_2O): 1.16 (*d*, $J = 7$, 3H, $\text{CH}_3\text{-C}(2)$); 1.5–2.1 (*m*, 2H, $2\text{H-C}(3)$); 3.1–3.4 (*m*, 2H, $2\text{H-C}(4)$); 3.63 (*s*, 3H, CH_3O); 3.4–3.8 (*m*, 1H, $\text{H-C}(2)$); 7.8 (*m*, 15H).

1.2.3. Methyl (2*RS*, 4*EZ*)-5-[3',5'-bis(benzyloxy)phenyl]-2-methyl-4-pentenoate (**5**). K (350 mg, 9 mmol) was reacted with dry 2-methyl-2-butanol (15 ml). The excess alcohol was distilled off and the alcoholate was dissolved in

15 ml of hexamethylphosphoric triamide. At 0°, a solution of 4.27 g (8.5 mmol) of **3** in 20 ml of dry DMF was added with simultaneous formation of the orange ylide. After 15 min, a solution of 2.0 g (6.3 mmol) of 3,5-bis(benzyloxy)benzaldehyde (**1**) in 20 ml of benzene was introduced. The mixture was stirred for 2 h at 23° and partitioned between Et₂O/H₂O. The crude product obtained from the Et₂O-phase was dissolved in 50 ml of CCl₄, and the Ph₃PO was precipitated by addition of 300 ml of petroleum ether. Chromatography of the product on 200 g of silica gel (fract. size 200 ml, toluene/petroleum ether 2:1) yielded 1.316 g (37% calc. on **3**) of pure **5** (fract. 18–27). Analytical data: see [1].

1.2.4. Transformations from **5** to **7**, **7** to **10** and **10** to **12**. See [1].

1.3. *Amide 16 from 12*. A solution of 589 mg (2.86 mmol) of dicyclohexylcarbodiimide (DCC) in 15 ml of abs. MeCN was added dropwise at 0° to 1.025 g (2.86 mmol) of **12** and 329 mg (2.86 mmol) of *N*-hydroxysuccinimide in 13 ml of abs. MeCN. Precipitation of dicyclohexylurea started immediately. The mixture was stirred at 23° for 24 h, the urea removed by filtration and solvent removed *in vacuo*. The crude ester **14** was dissolved in 16 ml of dioxane and added at 23° to a solution of 420 mg of NaHCO₃ and 255 µl of EtNH₂ (70% in H₂O; 3.15 mmol) in 35 ml of H₂O/dioxane 3:2. Stirring was continued for 90 min, the solvent removed *in vacuo*, and the residue partitioned between Et₂O/H₂O. The crude product resulting from the org. phase was adsorbed to 10 g of silica gel and chromatographed on 90 g of silica gel (fract. size 100 ml; fract. 1–20 Et₂O/petroleum ether 1:1, fract. 20–40 Et₂O). Fract. 21–27 yielded 887 mg (77%) of pure **16**. ¹H-NMR (cf. Fig. 2): 1.068 (*s*, 3H, 3H-C(13)); 1.098 (*d*, *J* = 6, 3H, CH₃-C(17)); 1.098 (*t*, *J* = 7, 3H, NCH₂CH₃); 1.36 (*s*, 3H, 3H-C(12)); 1.41 (*m*, 2H-C(16)); 1.54 (*quint.*, *J* = 7, 2H, 2H-C(15)); 1.68 (*s*, 3H, 3H-C(11)); 1.78 (*m*, 3H, H-C(6a), H_α-C(7), H_β-C(10)); 2.14 (*m*, 2H, H_β-C(7), H-C(17)); 2.42 (*m*, 2H, 2H-C(14)); 2.71 (*dt*, *J* = 5, 11, 1H, H-C(10a)); 3.27 (1H, H_α-C(10)); 3.27 (*dq*, *J* = 7, 7, NCH₂CH₃); 5.41 (*br. s*, 1H, H-C(8)); 5.58 (*t*, *J* = 7, NH); 6.15, 6.18 (2*d*, *J* = 2 each, 2H, H-C(2), H-C(4)). MS: see Fig. 1, values in italics.

1.4. *Amide 15 from 11*. As described in 1.3, 356 mg (0.98 mmol) of **11** were reacted with 110 mg (0.95 mmol) of *N*-hydroxysuccinimide and 196 mg (0.95 mmol) of DCC. The crude ester **13** was treated with 120 mg of NaHCO₃ and 80 µl of 70% EtNH₂. Chromatography on silica gel yielded 308 mg (80%) of pure **15**. ¹H-NMR: same signals as **16** except for CH₃-C(17), H-C(17) and H-C(16). MS: see Fig. 1.

2. (6*aR*,10*aR*)-17,18-Didehydro- Δ^8 -tetrahydrocannabinol (= (6*aR*,10*aR*)-6,6,9-Trimethyl-3-(4-pentenyl)-6*a*,7,10,10*a*-tetrahydro-6*H*-dibenzo[*b*,*d*]pyran-1-ol; **23**) and (6*aR*,10*aR*)-[17,18-²H₂]- Δ^8 -Tetrahydrocannabinol (= (6*aR*,10*aR*)-6,6,9-Trimethyl-3-(4,5-²H₂]pentenyl)-6*a*,7,10,10*a*-tetrahydro-6*H*-dibenzo[*b*,*d*]pyran-1-ol; **24**).

2.1. 1-(3',5'-Dimethoxyphenyl)-5-phenoxy-1-pentene (**19**). A solution of 2.6 ml (≈ 4.2 mmol) of BuLi in hexane was added dropwise at 0° to a suspension of 2.0 g (4.1 mmol) of (4-phenoxybutyl)triphenylphosphonium bromide (**18**) in 50 ml of dry Et₂O. After stirring the red mixture for 30 min at 0°, a solution of 0.70 g (4.2 mmol) of 3,5-dimethoxybenzaldehyde (**17**) in 20 ml of Et₂O was slowly introduced. A pale yellow precipitate (Ph₃PO) formed, the mixture was allowed to warm up to 23°, and, after addition of 30 ml of Et₂O, was heated under reflux for 2 h. The solvent was removed *in vacuo* and the crude product partitioned between petroleum ether/H₂O. The product contained in the org. phase was chromatographed on silica gel (200 g; fract. size 200 ml; fract. 1–10 petroleum ether/Et₂O 98:2, fract. 11–20 petroleum ether/Et₂O 95:5). Fract. 12 and 13 gave 230 mg of pure (*Z*)-**19**, fract. 14–19 530 mg of (*E/Z*)-**19** (together 62% yield). ¹H-NMR ((*Z*)-**19**): 1.95 (*quint.*, 2H, 2H-C(4)); 2.5 (*q*, 2H, 2H-C(3)); 3.8 (*s*, 6H, 2CH₃O); 4.0 (*t*, *J* = 7, 2H, 2H-C(5)); 5.7 (*dt*, *J* = 11.4, 7, 1H, H-C(2)); 6.2–7.4 (*div. m*, 9H). MS: 298 (100, *M*⁺), 205 (83, *M*⁺–OC₆H₅), 191 (59, *M*⁺–CH₂OC₆H₅), 178 (76, *M*⁺–H₂C=CHOC₆H₅); 151 (36, *M*⁺–H₂C=CHOC₆H₅–C₂H₅).

2.2. 1-(3',5'-Dimethoxyphenyl)-5-phenoxy-pentane (**20**). Compound **19** (1.732 g, 5.81 mmol) was hydrogenated at 1.5 atm/23° over 10% Pd/C (200 mg) in 60 ml of EtOH for 1 h. The catalyst was removed by filtration and the solvent evaporated *in vacuo*: 1.656 g (95%) of pure **20**. ¹H-NMR: 1.5–2.0 (*m*, 6H, 2H-C(2), 2H-C(3), 2H-C(4)); 2.62 (*t*, *J* = 7, 2H, 2H-C(1)); 3.82 (*s*, 6H, 2CH₃O); 3.97 (*t*, *J* = 7, 2H, 2H-C(5)); 6.4 (*m*, 3H, H-C(2'), H-C(4'), H-C(6')); 6.8–7.4 (*m*, 5H, OC₆H₅). MS: 300 (34, *M*⁺); 207 (22, *M*⁺–OC₆H₅); 152 (100, *M*⁺–H₂C=CHCH₂OC₆H₅); 151 (62, *M*⁺–H₂CCH₂CH₂OC₆H₅).

2.3. 5-(5'-Bromopentyl)resorcinol (**21**). BBr₃ (0.83 ml; 8.7 mmol) in 30 ml of dry benzene was added dropwise at 10° to a stirred solution of 2.476 g (8.3 mmol) of **20** in 100 ml of dry benzene. Stirring was continued at 23° for 48 h with successive addition of BBr₃ (0.63 ml (16 h), 0.42 ml (18 h) and 0.2 ml (23 h)). The mixture was poured on 100 ml of ice H₂O and the org. phase was washed twice with 100 ml of 5% NaHSO₃. The solvent was removed *in vacuo* and the residue taken up in 10 ml of acetone and 100 ml of H₂O. Extraction with benzene yielded crude **21** that was chromatographed on silica gel (200 g; fract. size 200 ml; fract. 1–10 petroleum ether/CH₂Cl₂ 1:1, fract. 11–20

CH_2Cl_2 , fract. 21–30 $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ 9:1). Fract. 21–28 gave 1.738 g (80.8%) of pure **21**. $^1\text{H-NMR}$: 1.2–2.05 (*m*, 6H, 2H–C(2'), 2H–C(3'), 2H–C(4')); 2.53 (*t*, *J* = 7, 2H, 2H–C(1')); 3.42 (*t*, *J* = 6, 2H, 2H–C(5')); 5.18 (br. *s*, 2H, 2OH); 6.25 (*s*, 3H, H–C(2), H–C(4); H–C(6)). MS: 258 and 260 (7 and 7', resp., M^+), 179 (55, M^+ – Br), 124 (85, M^+ – Br – C_4H_7), 123 (100, M^+ – Br – C_4H_8).

2.4. (6*aR*, 10*aR*)-18-Bromo- Δ^8 -tetrahydrocannabinol (= (6*aR*, 10*aR*)-3-(5-Bromopentyl)-6,6,9-trimethyl-6*a*,7,10,10*a*-tetrahydro-6*H*-dibenzo[*b,d*]pyran-1-ol; **22**). A mixture of 1.39 g (5.37 mmol) of **21**, 1.06 g **8** (Firmenich, New York) and 200 mg of p-TsOH · H_2O in 75 ml of dry benzene was heated under reflux for 4 h. The solvent was removed *in vacuo*. The residue was dissolved in 100 ml of Et_2O , washed with 10% NaHCO_3 and H_2O (3 ×). The crude product resulting from the Et_2O phase was chromatographed on silica gel (200 g; fract. size 200 ml; fract. 1–20 petroleum ether/ CH_2Cl_2 9:1, 21–30 8:2, 31–40 6:4) to give 800 mg (38.0%) of pure **22** (fract. 31–37). $^1\text{H-NMR}$: 1.2 (*s*, 3H, 3H–C(13)); 1.4 (*s*, 3H, 3H–C(12)); 1.73 (br. *s*, 3H, 3H–C(11)); 2.48 (*t*, *J* = 6, 2H, 2H–C(14)); 2.7 (*m*, 1H, H–C(10*a*)); 3.22 (*dd*, *J* = 16, 4, 1H, H_α –C(10)); 3.42 (*t*, *J* = 7, 2H, 2H–C(18)); 4.73 (*s*, 1H, OH); 5.45 (br. *s*, 1H, H–C(8)); 6.1 (*d*, *J* = 2, 1H, H–C(2)); 6.28 (*d*, *J* = 2, 1H, H–C(4)). MS: 394, 392 (25, M^+); 379, 377 (6, M^+ – CH_3); 351, 349 (24, M^+ – C_3H_7); 326, 324 (6, M^+ – 68); 313 (100, M^+ – Br); 311, 309 (49, M^+ – 68 – 15); 258 (22, M^+ – $\text{C}_4\text{H}_7\text{Br}$); 257 (8, M^+ – $\text{C}_4\text{H}_8\text{Br}$).

2.5. 17,18-Didehydro Compound **23**. A 0.15 M solution (52 ml) of potassium 3-ethyl-3-pentanoate in xylene was added under stirring to 860 mg (2.2 mmol) of **22** in 20 ml of dry benzene. The mixture was heated for 19 h at 70°, cooled, and saturated with CO_2 for 30 min. After addition of 30 ml of benzene, the mixture was extracted with H_2O (3 × 100 ml), the solvent evaporated *in vacuo*, and the residue was purified by column chromatography on silica gel (100 g; fract. size 100 ml; petroleum ether/ CH_2Cl_2 3:7). Fract. 3–6 gave 285 mg of crude **23** that was further purified on silica gel (35 g; fract. size 35 ml; fract. 1–20 petroleum ether/toluene 9:1, 21–30 petroleum ether/toluene 3:1, 31–40 petroleum ether/toluene/ CH_2Cl_2 5:1:4). Fract. 34–36 yielded 228 mg of **23**, still containing impurities. Final purification was achieved on silica gel/ AgNO_3 9:1 (35 g; fract. size 35 ml; fract. 1–10 petroleum ether/ Et_2O 98:2, 11–20 95:5, 21–30 90:10, 31–40 80:20, 41–60 60:40). Fract. 45–49 gave 92 mg (14%) of pure **23**. $^1\text{H-NMR}$: see Fig. 3. MS: 312 (83, M^+), 297 (7, M^+ – 15), 269 (24, M^+ – 43), 258 (100, M^+ – C_4H_6), 243 (8, M^+ – C_4H_6 – CH_3), 229 (73, M^+ – 68 – 15).

2.6. Dideuterio Compound **24**. A solution of 30 mg of **23**, 8.5 mg of $[(\text{C}_6\text{H}_5)_3\text{P}]_3\text{RuCl}_2$ (Fluka) and 1.5 μl of Et_3N in 1.5 ml of benzene was treated with $^2\text{H}_2$ at 3 atm for 24 h at 23° (no starting material left). The catalyst was removed by chromatography on aluminium oxide (neutral, act. III; 7 g; fract. size 7 ml; petroleum ether/ CH_2Cl_2 3:1). Fract. 49–82 yielded **24** (16 mg) that was rechromatographed on Florisil (5 g; fract. size 5 ml; toluene) to give 15 mg (49%) of pure **24** (fract. 2–12). $^1\text{H-NMR}$: 0.9 (*m*, 2H, 2H–C(18)); 1.12 (*s*, 3H, 3H–C(13)); 1.38 (*s*, 3H, 3H–C(12)); 1.72 (br. *s*, 3H, 3H–C(11)); 2.48 (*t*, *J* = 8, 2H, 2H–C(14)); 2.75 (*m*, 1H, H–C(10*a*)); 3.22 (*dd*, *J* = 17, 4, 1H, H_α –C(10)); 5.43 (br. *s*, 1H, H–C(8)); 6.11 (*d*, *J* = 2, 1H, H–C(2)); 6.28 (*d*, *J* = 2, 1H, H–C(4)). MS: 316 (M^+).

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