256. Synthesis of Cannabinoid Model Compounds

Part 3[1])

(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/Et_3N using $[(C_6H_5)_3P]_3RuCl_2$ as catalyst.

Recently, we have reported the synthesis of (6a*R*, 10a*R*)-Δ^8-tetrahydrocannabinol-18-oic acid[2]) (= 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.

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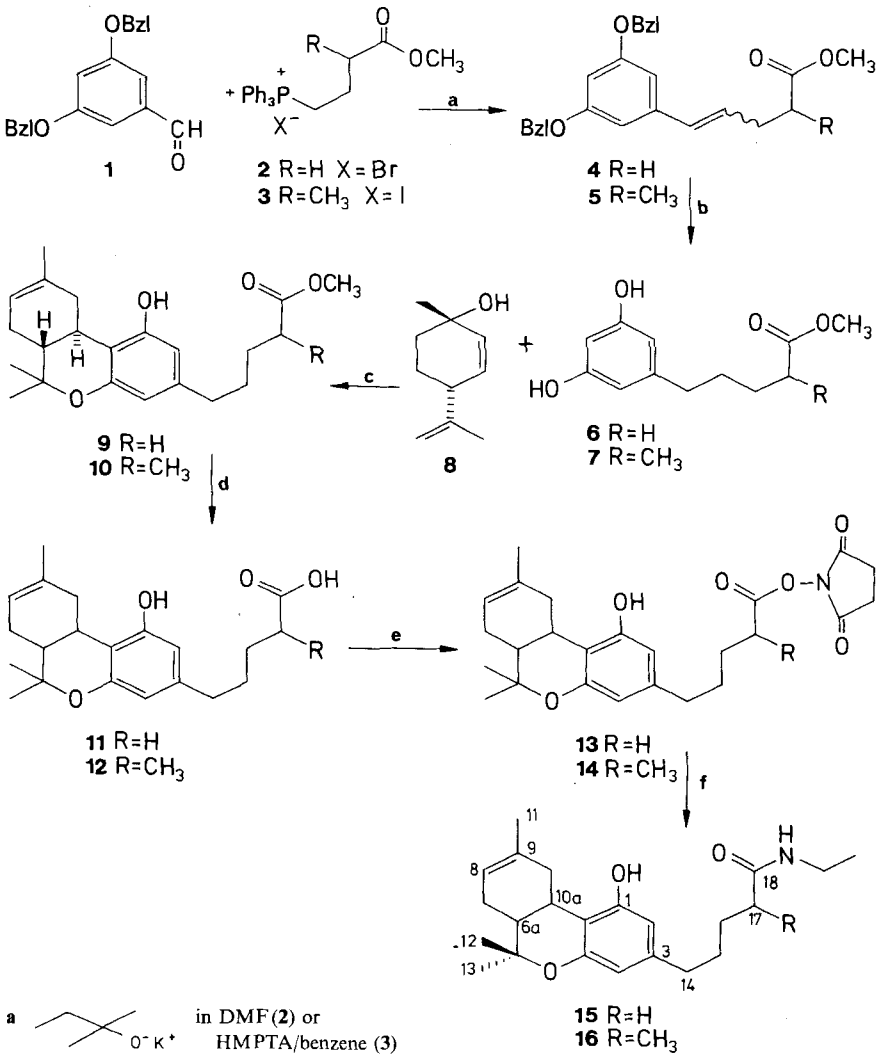
[1]) Part 2: see [1].

[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.

Characterization of Δ^9-THC-binding sites requires radiolabelled ligands of high specific activity and 17,18-didehydro-Δ^8-THC (**23**) was chosen as precursor for the synthesis of [17,18-$^3H_2$]-Δ^8-THC (**24**). This paper describes also the synthesis of **23** and **24**.

Scheme 1

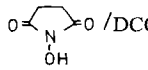


a in DMF (**2**) or HMPTA/benzene (**3**)

b H_2/Pd · AcOEt

c TsOH, benzene

d KOH/MeOH

e  /DCC · MeCN

f $EtNH_2$/dioxane H_2O

1. Syntheses of Amides **15** *and* **16** *(Scheme 1).* – Basically, the acids **11** and **12** were obtained as described in [1] (**1** + **2** → **4** → **6**(+ **8**) → **9** → **11**; **1** + **3** → **5** → **7**(+ **8**) → **10** → **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 $EtNH_2$ in aqueous dioxane.

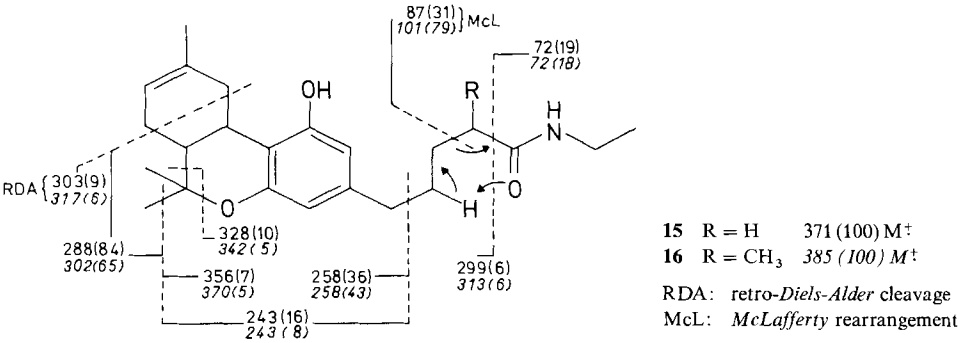


Fig. 1. *Fragments* (m/z) *in the MS of the Amides* **15** *and* **16**. Values of **16** in italics, relative intensities in parentheses.

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 ^{1}H-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 ^{1}H-NMR spectra of tetrahydrocannabinols have been analyzed in detail [8] only signals relevant to the substituted side chain will be discussed here. The CH_3CH_2NHCO-function gives rise to a *dq* (CH_3CH_2) centered at 3.28 and 3.25, a *t* at 5.58 (NH), and a *t* at 1.1 ppm (CH_3CH_2). 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 2 H–C(16) at 1.41 ppm. The CH_3–C(17) leads to a *d* at 1.1 ppm. By decoupling at this position, H–C(17) was located at 2.14 ppm.

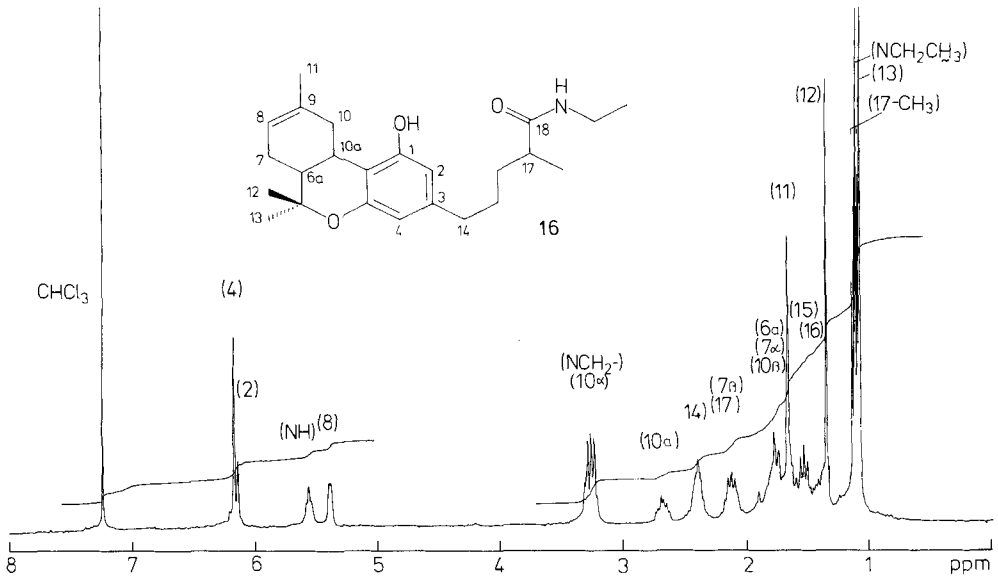
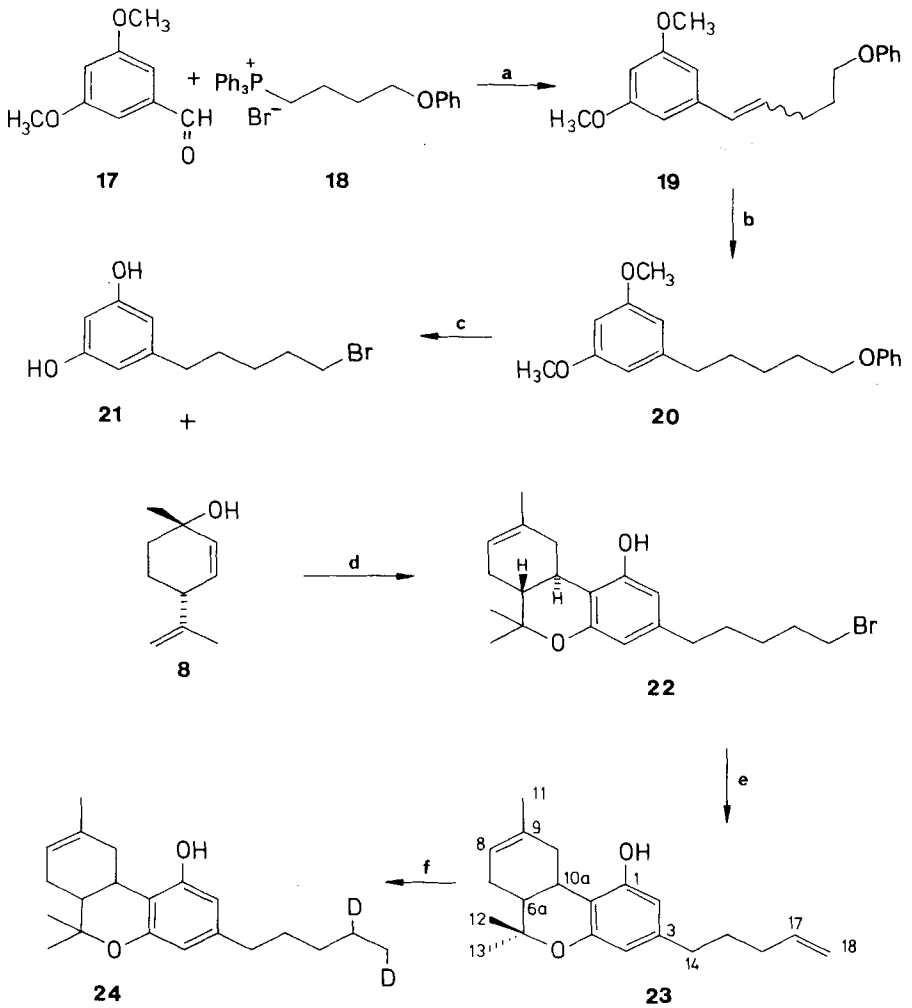


Fig. 2. *250-MHz ^{1}H-NMR Spectrum of (6a*R*, 10a*R*, 17*RS*)-N-Ethyl-17-methyl-Δ^8-tetrahydrocannabinol-18-amide* (**16**) *in $CDCl_3$*

2. Synthesis of 17,18-Didehydro-Δ^8-THC (**23**) and *[17,18-$^2H_2$]-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 proceded 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 (6a*R*, 10a*R*)-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 $[(C_6H_5)_3P]_3RuCl_2$ to give [17,18-$^2H_2$]-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 ^{1}H-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^+-C_4H_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 $BuLi/Et_2O$
b $H_2/Pd/C$, EtOH
c BBr_3/benzene
d TsOH/benzene
e $Et_3CO^-K^+$/toluene, benzene
f $D_2/[(C_6H_5)_3P]_3RuCl_2$, Et_3N/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 Δ^8-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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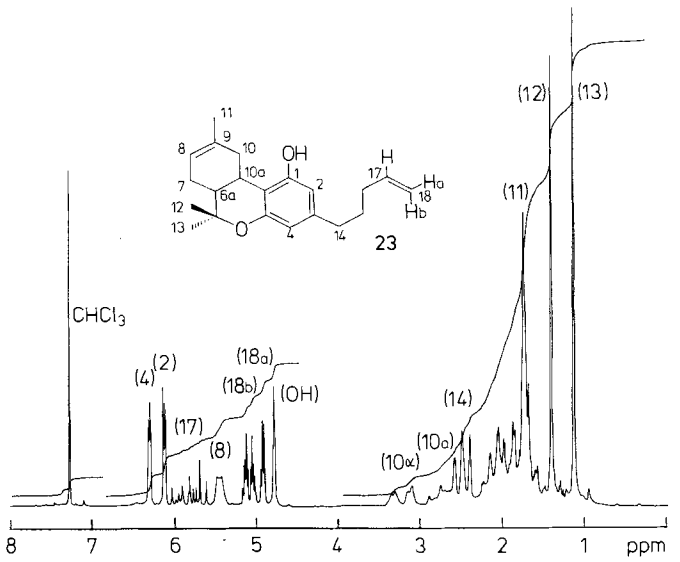

Fig. 3. *80-MHz ^{1}H-NMR Spectrum of 17, 18-Didehydro-Δ^8-THC* (**23**) *in $CDCl_3$*

Experimental Part

General Remarks. See [1].

1. (*6aR,10aR*)-N-*Ethyl-Δ^8-tetrahydrocannabinol-18-amide* (= N-*Ethyl-5-*[(*6aR,10aR*)-*1-hydroxy-6,6,9-trimethyl-6a,7,10,10a-tetrahydro-6*H-*dibenzo*[b,d]*pyran-3-yl*]*pentanamide*; **15**) *and* (*6aR,10aR,17*RS)-N-*Ethyl-17-methyl-Δ^8-tetrahydrocannabinol-18-amide* (= (*2*RS)-N-*Ethyl-5-*[(*6aR,10aR*)-*1-hydroxy-6,6,9-trimethyl-6a,7,10,10a-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. (*6aR,10aR*)-*Δ^8-Tetrahydrocannabinol-18-oic Acid* (= 5-[(*6aR,10aR*)-*1-Hydroxy-6,6,9-trimethyl-6a,7,10,10a-tetrahydro-6*H-*dibenzo*[b,d]*pyran-3-yl*]*pentanoic Acid*; **11**). See [1].

1.2. (*6aR,10aR,17*RS)-*17-Methyl-Δ^8-tetrahydrocannabinol-18-oic Acid* (= (*2*RS)-*5-*[(*6aR,10aR*)-*1-Hydroxy-6,6,9-trimethyl-6a,7,10,10a-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 (*2RS*)-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 Et_2O/H_2O. The org. phase yielded 2.62 g (98%) of pure methyl 4-iodo-2-methylbutanoate. ^{1}H-NMR: 1.17 (*d*, *J* = 7, 3H, CH_3–C(2)); 1.7 (*m*, 2H, 2H-C(3)); 2.4–2.8 (*m*, 1H, H–C(2)); 3.20 (*t*, *J* = 6, 2H, 2H–C(4)); 3.61 (*s*, 3H, CH_3O). MS: 211 (13, M^+–OCH_3), 183 (9, M^+–$COOCH_3$), 155 (6, M^+–$CH(CH_3)COOCH_3$), 115 (75, M^+–I), 88 (16, $CH_3CH{=}C(OH)OCH_3^+$), 59 (100, $COOCH_3^+$).

1.2.2. (*3-(Methoxycarbonyl)butyl)triphenylphosphonium Iodide* (**3**). A solution of 2.62 g (10.8 mmol) of methyl (*2RS*)-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 × with benzene (30 ml) and dried at 0.01 Torr: 4.27 g (98%). ^{1}H-NMR ((D_6)DMSO): 1.16 (*d*, *J* = 7, 3H, CH_3–C(2)); 1.5–2.1 (*m*, 2H, 2H–C(3)); 3.1–3.4 (*m*, 2H, 2H–C(4)); 3.63 (*s*, 3H, CH_3O); 3.4–3.8 (*m*, 1H, 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 destilled off an 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 Et_2O/H_2O. The crude product obtained from the Et_2O-phase was dissolved in 50 ml of CCl_4, and the Ph_3PO 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 dicylohexylurea 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 $NaHCO_3$ and 255 µl of $EtNH_2$ (70% in H_2O; 3.15 mmol) in 35 ml of H_2O/dioxane 3:2. Stirring was continued for 90 min, the solvent removed *in vacuo*, and the residue partitioned between Et_2O/H_2O. 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 Et_2O/petroleum ether 1:1, fract. 20–40 Et_2O). Fract. 21–27 yielded 887 mg (77%) of pure **16**. ^{1}H-NMR (*cf. Fig. 2*): 1.068 (*s*, 3H, 3H–C(13)); 1.098 (*d*, $J = 6$, 3H, CH_3–C(17)); 1.098 (*t*, $J = 7$, 3H, NCH_2CH_3); 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*, $J = 7, 7$, NCH_2CH_3); 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 $NaHCO_3$ and 80 µl of 70% $EtNH_2$. Chromatography on silica gel yielded 308 mg (80%) of pure **15**. ^{1}H-NMR: same signals as **16** except for CH_3–C(17), H–C(17) and H–C(16). MS: see *Fig. 1*.

2. *(6aR,10aR)-17,18-Didehydro-Δ^8-tetrahydrocannabinol (= (6aR,10aR)-6,6,9-Trimethyl-3-(4-pentenyl)-6a,7,10,10a-tetrahydro-6*H*-dibenzo*[b,d]*pyran-1-ol*; **23**) *and (6aR,10aR-[17,18-$^2H_2$]-Δ^8-Tetrahydrocannabinol (= (6aR,10aR)-6,6,9-Trimethyl-3-([4,5-$^2H_2$]pentyl)-6a,7,10,10a-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 Et_2O. 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 Et_2O was slowly introduced. A pale yellow precipitate (Ph_3PO) formed, the mixture was allowed to warm up to 23°, and, after addition of 30 ml of Et_2O, was heated under reflux for 2 h. The solvent was removed *in vacuo* and the crude product partitioned between petroleum ether/H_2O. The product contained in the org. phase was chromatographed on silica gel (200 g; fract. size 200 ml; fract. 1–10 petroleum ether/Et_2O 98:2, fract. 11–20 petroleum ether/Et_2O 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). ^{1}H-NMR ((*Z*)-**19**): 1.95 (*quint.*, 2H, 2H–C(4)); 2.5 (*q*, 2H, 2H–C(3)); 3.8 (*s*, 6H, $2CH_3O$); 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, $M^+ - OC_6H_5$), 191 (59, $M^+ - CH_2OC_6H_5$), 178 (76, $M^+ - H_2C=CHOC_6H_5$); 151 (36, $M^+ - H_2C=CHOC_6H_5 - C_2H_3$).

2.2. *1-(3',5'-Dimethoxyphenyl)-5-phenoxypentane* (**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**. ^{1}H-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, $2CH_3O$); 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, OC_6H_5). MS: 300 (34, M^+); 207, (22, $M^+ - OC_6H_5$); 152 (100, $M^+ - H_2C=CHCH_2OC_6H_5$); 151 (62, $M^+ - H_2CCH_2CH_2OC_6H_5$).

2.3. *5-(5'-Bromopentyl)resorcinol* (**21**). BBr_3 (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 BBr_3 (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 H_2O and the org. phase was washed twice with 100 ml of 5% $NaHSO_3$. The solvent was removed *in vacuo* and the residue taken up in 10 ml of acetone and 100 ml of H_2O. Extraction with benzene yielded crude **21** that was chromatographed on silica gel (200 g; fract. size 200 ml; fract. 1–10 petroleum ether/CH_2Cl_2 1:1, fract. 11–20

CH_2Cl_2, fract. 21–30 CH_2Cl_2/Et_2O 9:1). Fract. 21–28 gave 1.738 g (80.8%) of pure **21**. ^{1}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. *(6aR,10aR)-18-Bromo-Δ^8-tetrahydrocannabinol (= (6aR,10aR)-3-(5-Bromopentyl)-6,6,9-trimethyl-6a,7,10,10a-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}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(10a)); 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, $M^+ - C_4H_7Br$); 257 (8, $M^+ - C_4H_8Br$).

2.5. *17,18-Didehydro Compound* **23**. A 0.15 M solution (52 ml) of potassium 3-ethyl-3-pentanolate 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}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 $[(C_6H_5)_3P]_3RuCl_2$ *(Fluka)* and 1.5 µl of Et_3N in 1.5 ml of benzene was treated with $^2H_2$ 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}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(10a)); 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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