Pharmacophoric Requirements for Cannabinoid Side Chains. Naphthoyl and Naphthylmethyl Substituted Δ^8-Tetrahydrocannabinol Analogs

Demetris P. Papahatjis* and Therapia Kourouli

National Hellenic Research Foundation, Institute of Organic and Pharmaceutical Chemistry, Athens 116-35, Greece

Alexandros Makriyannis*

Departments of Pharmaceutical Sciences, Molecular and Cell Biology and Institute of Materials Science, Storrs, CT 06269 USA

Received February 13, 1996

In memory of Professor Nicholas Alexandrou

We have synthesized hybrids of classical cannabinoids and aminoalkylindoles by combining the dibenzopyran structure of Δ^8-tetrahydrocannabinol with the ketonaphthyl or 1-naphthylmethyl moieties found in aminoalkylindoles in order to investigate the role of the ketonaphthyl and 1-naphthylmethyl pharmacophores in cannabimimetic activity.

J. Heterocyclic Chem., **33**, 559 (1996).

Introduction.

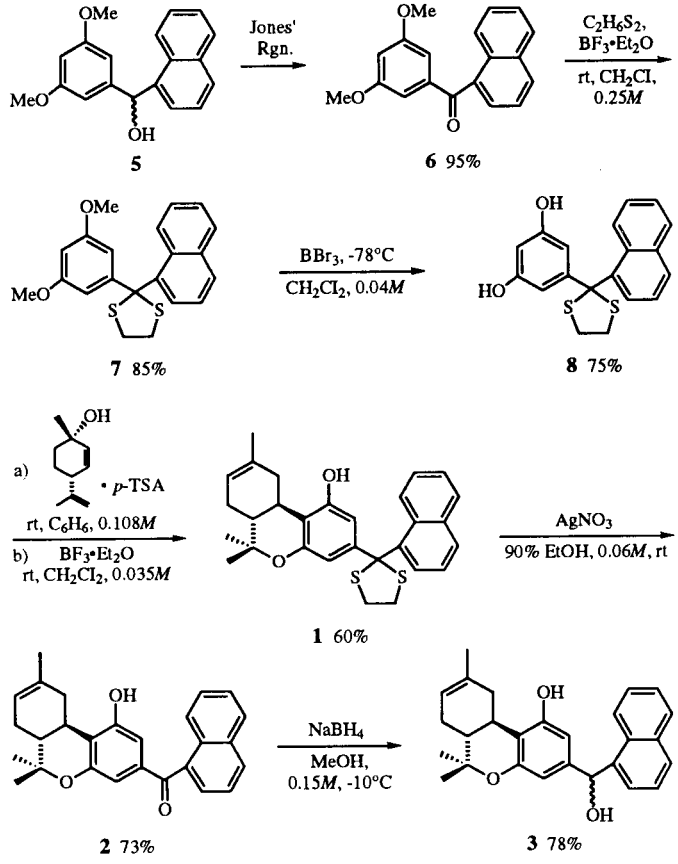
The major psychoactive component of cannabis, Δ^9-tetrahydrocannabinol, as well as the putative endogenous ligand for the cannabinoid receptor, anandamide [1] mediate their cellular effects through a specific G protein-coupled receptor in the brain (CB1) [2]. Recently a novel cannabinoid receptor, designated as CB2 has been described [3]. The CB2 subtype was shown to be expressed in the spleen and may be involved in cannabinoid-mediated immune response.

The need for establishing structure-activity relationships for cannabinoid activity led to the synthesis of numerous classical-cannabinoid analogs with high cannabimimetic activity [4] and several 3-arylcyclohexanol, non-classical cannabinoids, such as CP-55,940 [5]. More recently, several aminoalkylindole analogs such as WIN-55212-2 with no obvious structural similarity to the cannabinoids were shown to possess cannabimimetic properties [2,6]. These aminoalkylindole analogs display excellent cannabinoid activity *in vitro*, as well as, *in vivo* and appear to bind at the same site of the cannabinoid receptor.

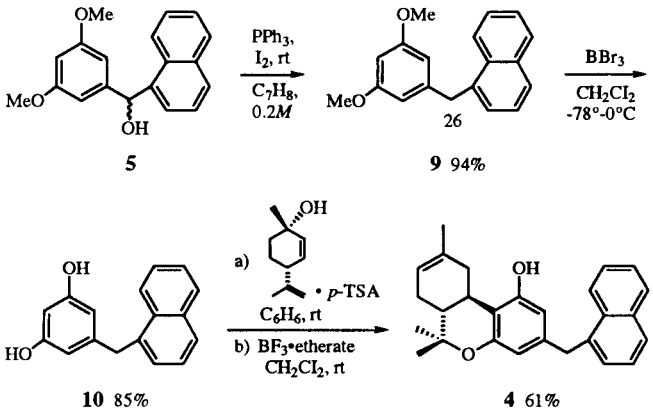
The most potent of the aminoalkylindole analogs share three common features: (a) an indole ring system; (b) a tertiary amine moiety; and (c) an α-naphthoyl group. In contrast, the potent classical cannabinoid analogs contain: (a) a phenolic moiety; (b) a cyclohexyl ring; and (c) a hydrophobic side chain.

Recently, when investigating the pharmacophoric similarities between the aminoalkylindole analogs and the classical cannabinoid analogs, by using 2D nmr spectroscopy in combination with computer-assisted molecular modeling, we proposed a model in which the naphthoyl, morpholino, and 3-keto groups in the aminoalkylindole analogs, correspond to the side chain, cyclohexyl ring and phenolic hydroxyl of the classical cannabinoid analogs, respectively [7]. To test this hypothesis, we synthesized hybrids of classical cannabinoids and aminoalkylindoles by combining the dibenzopyran structure of Δ^8-tetrahydrocannabinol with the ketonaphthyl or 1-naphthylmethyl moieties found in aminoalkylindole analogs as described in this communication. The synthesis of analogs (**1-4**),

Scheme 1



Scheme 2



(Schemes 1 and 2) and their *in vitro* pharmacological evaluation will help to explore the structural requirements for cannabinoid activity and serve as a basis for future drug design.

Results and Discussion.

All of the Δ^8-tetrahydrocannabinoid analogs were synthesized by the condensation of (+)-*cis/trans-p*-mentha-2,8-dien-1-ol with the appropriately substituted resorcinol by the sequential treatment with *p*-toluenesulfonic acid and boron trifluoride etherate. The aromatic coupling partner **8** was prepared from commercially available 3,5-dimethoxybenzaldehyde by a four step reaction sequence as depicted in Scheme 1. The initial Grignard reaction between 1-naphthalenemagnesium bromide and 3,5-dimethoxybenzaldehyde provided hydroxy compound **5** in 90% yield. Treatment of **5** with Jones' reagent at room temperature, followed by exposure of the resulting ketone **6** to 1,2-ethanedithiol in the presence of borontrifluoride etherate resulted in the formation of 2-[3,5-dimethoxybenzene]-2-[naphthyl]-1,3-dithiolane (**7**). The methoxy linkages of **7** were cleaved with boron tribromide in methylene chloride to afford 2-[3,5-dihydroxybenzene]-2-[naphthyl]-1,3-dithiolane (**8**) in 75% yield. Finally condensation with (+)-*cis/trans-p*-mentha-2,8-dien-1-ol provided the cannabinoid derivative **1**.

Compound **1** lent itself to conversion to cannabinoid analogs **2** and **3**. Thus cleavage of the 1,3-dithiolane protecting group with silver nitrate [8] afforded 3-ketonaphthyl derivative 2, which was subsequently reduced to the corresponding cannabinoid analog **3** in 78% yield.

For the preparation of the resorcinol derivative **9** (Scheme 2), substitution of the hydroxyl group by hydrogen *via* the corresponding iodo intermediate was initially planned. However, the direct replacement of the hydroxyl by iodine according to the well known triphenylphosphine/iodine/imidazole method, when performed in the absence of imidazole [9], afforded the naphthylmethyl compound **9** in 94% yield. Dimethyl ether cleavage, followed by condensation with (+)-*cis/trans-p*-mentha-2,8-dien-1-ol generated the target cannabinoid **4**.

The cannabinoids **1-4** were evaluated *in vitro* by using standard cannabinoid assays as described by Compton [10]. All analogs were found to possess cannabimimetic activity although their potencies were lower than those of the parent cannabinoid Δ^8-tetrahydrocannabinol. These results will be described in more detail elsewhere.

EXPERIMENTAL

All reactions were carried out under scrupulously dry conditions with magnetic stirring. Organic phases were dried over anhydrous sodium sulfate and evaporated under reduced pressure. Silica gel (grade 60, 200-400 mesh, E. Merck, Germany) and (ASTM 150-230 mesh, E. Merck, Germany) was used for flash and gravity column chromatography respectively. All compounds were demonstrated to be homogeneous by analytical tlc on precoated silica gel tlc plates (grade 60, F254, E. Merck, Germany), and chromatograms were visualized by phosphomolybdic acid staining. The ^{1}H nmr spectra were recorded on a Bruker AC 300 spectrometer operating at 300 MHz and are reported in units of δ relative to internal chloroform at 7.24 ppm. All nmr spectra were recorded in deuteriochloroform unless otherwise stated. Analyses indicated by the symbols of the elements were carried out by the microanalytical section of the Institute of Organic and Pharmaceutical Chemistry of the National Hellenic Research Foundation.

α-(3,5-Dimethoxybenzene)-α-(1-naphthalene)methanol (**5**).

3,5-Dimethoxybenzaldehyde (0.60 g, 3.61 mmoles) was dissolved in dry tetrahydrofuran (7.22 ml), an argon atmosphere was secured and the flask cooled to -78°. 1-Naphthalenemagnesium bromide [prepared from 1-bromonaphthalene (1.5 ml, 10.83 mmoles) and Mg turnings (0.263 g, 10.83 mmoles) in dry tetrahydrofuran (20 ml)] was added and stirring continued for 4 hours at -60°. Upon completion the reaction was quenched by the addition of saturated ammonium chloride (10 ml). The reaction mixture was extracted with ethyl acetate (3 x 20 ml), washed with saturated ammonium chloride (2 x 10 ml), brine (10 ml), dried (anhydrous sodium sulfate) and evaporated. Purification by flash column chromatography (20% diethyl ether-petroleum ether as eluent) provided 0.95 g of compound **5** (90%) as an oil; ^{1}H nmr (300 MHz, deuteriochloroform): δ 8.09-8.05 (m, 1H, naphthalene proton), 7.86-7.78 (m, 2H, naphthalene protons), 7.58 (d, J = 7 Hz, 1H, naphthalene proton), 7.48-7.43 (m, 3H, naphthalene protons), 6.57 (d, J = 2.1 Hz, 2H, phenyl protons), 6.44 (broad s, 1H, C*H*OH), 6.36 (t, J = 2.1 Hz, 1H, phenyl proton), 3.73 (s, 6H, OMe), 2.36 (broad s, 1H, OH).

Anal. Calcd. for $C_{19}H_{18}O_3$: C, 77.52; H, 6.16. Found: C, 78.00; H, 6.13.

1-(3,5-Dimethoxybenzoyl)naphthalene (**6**).

α-(3,5-Dimethoxybenzene)-α-(1-naphthalene)methanol (**5**) (0.11 g, 0.38 mmole) was dissolved in acetone (1 ml). To this cold (0°) solution was added a solution of Jones' reagent (0.53 ml, prepared from 7 g of chromium(VI) oxide, 50 ml water and 6.1 ml of concentrated sulfuric acid). The reaction mixture was

stirred at room temperature for 0.5 hour. Upon completion the reaction mixture was quenched by the addition of propan-2-ol (1 ml), diluted with ethyl acetate (20 ml) and the organic phase washed with 20% aqueous sodium bisulfite (2 x 5 ml), water (5 ml), brine (5 ml), dried (anhydrous sodium sulfate) and evaporated. Purification by flash column chromatography (30% diethyl ether-petroleum ether) yielded 104 mg of compound **6** (95%) as an oil; ^{1}H nmr (300 MHz, deuteriochloroform): δ 8.1-8.0 (m, 1H, naphthalene proton), 7.97-7.92 (m, 1H, naphthalene proton), 7.91-7.89 (m, 1H, naphthalene proton), 7.59-7.47 (m, 4H, naphthalene protons), 7.00 (d, J = 2.2 Hz, 2H, phenyl protons), 6.68 (t, J = 2.2 Hz, 1H, phenyl proton), 3.80 (s, 6H, OMe).

Anal. Calcd. for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52. Found: C, 78.00; H, 5.57.

2-[3,5-Dimethoxybenzene]-2-[1-naphthyl]-1,3-dithiolane (**7**).

Ketone **6** (0.109 g, 0.373 mmole) was dissolved in methylene chloride (1.5 ml) and 1,2-ethanedithiol (0.087 ml, 1.05 mmoles) was added, followed by borontrifluoride etherate (0.028 ml, 0.24 mmole). The solution was stirred at room temperature overnight and at completion a saturated solution of sodium hydrogen carbonate (1 ml) was added. The mixture was diluted with diethyl ether (20 ml). The organic layer was washed with water (5 ml), brine (2 x 5 ml), dried (anhydrous sodium sulfate) and evaporated to afford 117 mg of compound **7** (85%) sufficiently pure for the following step; ^{1}H nmr (300 MHz, deuteriochloroform): δ 8.38 (d, J = 7.3 Hz, 1H, naphthalene proton), 7.79-7.69 (m, 3H, naphthalene protons), 7.47-7.22 (m, 3H, naphthalene protons), 6.74 (d, J = 2.1 Hz, 2H, phenyl protons), 6.27 (t, J = 2.1 Hz, 1H, phenyl proton), 3.66 (s, 6H, OMe), 3.53-3.28 (m, 4H, SCH_2CH_2S).

Anal. Calcd. for $C_{21}H_{20}O_2S_2$: C, 68.45; H, 5.47. Found: C, 68.73; H, 5.42.

2-[3,5-Dihydroxybenzene]-2-[1-naphthyl]-1,3-dithiolane (**8**).

Boron tribromide (0.6 ml, 6.25 mmoles) was added to a solution of 2-[3,5-dimethoxybenzene]-2-[1-naphthyl]-1,3-dithiolane (**7**), (0.86 g, 2.33 mmoles) in methylene chloride (58 ml) at -78° under an argon atmosphere. Following the addition of boron tribromide the reaction temperature was raised gradually over a period of 3 hours to -30°. Stirring was continued at that temperature until completion of the reaction (48 hours). Unreacted boron tribromide was destroyed by addition of methanol at -78°. The methylene chloride was removed *in vacuo* and the residual oil was diluted with ethyl acetate. The solution was washed with saturated sodium hydrogen carbonate (2 x 20 ml), water (2 x 10 ml) and brine (2 x 20 ml). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by flash column chromatography (50% diethyl ether-petroleum ether as eluent) gave 600 mg of compound **8** (75%); oil; ^{1}H nmr (300 MHz, deuteriochloroform): δ 8.37 (d, J = 7.2 Hz, 1H, naphthalene proton), 7.79-7.76 (m, 2H, naphthalene protons), 7.7 (d, J = 8.5 Hz, 1H, naphthalene proton), 7.47-7.24 (m, 3H, naphthalene protons), 6.61 (d, J = 2.2 Hz, 2H, phenyl protons), 6.10 (t, J = 2.2 Hz, 1H, phenyl proton), 5.05 (broad s, 2H, O*H*), 3.49-3.29 (m, 4H, SCH_2CH_2S).

Anal. Calcd. for $C_{19}H_{16}O_2S_2$: C, 67.05; H, 4.74. Found: C, 67.37; H, 4.98.

2-[1-Hydroxy-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-6*H*-dibenzo[*b*,*d*]pyran-3-yl]-2-[1-naphthyl]-1,3-dithiolane (**1**).

To a solution of resorcinol **8** (0.51 g, 1.5 mmoles) in dry benzene (14.0 ml) at 25° under an argon atmosphere was added (+)-*cis*/*trans*-*p*-mentha-2,8-dien-1-ol (0.285 g, 1.87 mmoles), followed by the addition of *p*-toluenesulfonic acid (0.053 g, 0.28 mmole). The reaction mixture was stirred at 25° for 0.5 hour at which time thin-layer chromatography indicated the complete consumption of starting materials. The reaction mixture was diluted with ether. The ethereal solution was washed with saturated sodium hydrogen carbonate, water, brine and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by flash column chromatography (10% diethyl ether-petroleum ether) produced 0.707 g of cannabidiol. To a solution of this cannabidiol (0.707 g, 1.49 mmoles) in anhydrous dichloromethane (44 ml) was added borontrifluoride etherate (0.67 ml, 5.33 mmoles) at 0°. Following the addition, the reaction mixture was stirred at 25° for 4 hours, at which time tlc indicated the dissappearance of starting material. The reaction was quenched by the addition of a saturated solution of sodium hydrogen carbonate, concentrated *in vacuo* and diluted with ethyl acetate (100 ml). The organic layer was washed with water (15 ml), brine (2 x 15 ml) and dried over anhydrous sodium sulfate. Solvent evaporation and purification by flash column chromatography (10% diethyl ether-petroleum ether as eluent) provided cannabinoid analog **1**. The overall yield from **8** was 424 mg (60%); ^{1}H nmr (300 MHz, deuteriochloroform): δ 8.37 (d, J = 7.3 Hz, 1H, naphthalene proton), 7.76 (t, J = 7 Hz, 3H, naphthalene protons), 7.45-7.22 (m, 3H, naphthalene protons), 6.73 (d, J = 1.7 Hz, 1H, phenyl proton), 6.40 (d, J = 1.7 Hz, 1H, phenyl proton), 5.38 (d, J = 3.4 Hz, 1H, H_8), 4.8 (s, 1H, OH), 3.48-3.29 (m, 4H, SCH_2CH_2S), 3.28-3.26 (dd, J = 10 and 2 Hz, 1H, $H_{10\alpha}$), 2.7-2.59 (m, 1H, H_{10a}), 2.19-2.08 (m, 1H, H_7), 1.85-1.7 (m, 3H, $H_{6\alpha}$, H_7, H_{10b}), 1.64 (s, 3H, CH_3), 1.3 (s, 3H, CH_3), 1 09 (s, 3H, CH_3); ms: m/z 475 (M+1).

Anal. Calcd. for $C_{29}H_{30}O_2S_2$: C, 73.39; H, 6.37. Found: C, 73.46; H, 6.59.

1-Hydroxy-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-6*H*-dibenzo-[*b*,*d*]pyran-3-yl 1-Naphthyl Ketone (**2**).

To a stirred solution of **1** (46 mg, 0.096 mmole) in 90% ethanol (1.6 ml) at 25°, was added a solution of silver nitrate (42 mg, 0.24 mmole) in water (0.25 ml). The reaction mixture was stirred at room temperature for 3 hours. At completion the precipitate was removed, washed with ethyl acetate and the filtrate was further diluted with ethyl acetate. The acetate solution was washed with brine and dried over anhydrous sodium sulfate. Solvent evaporation and purification of the residue by flash column chromatography (15% diethyl ether-petroleum ether as eluent) afforded 28 mg of the cannabinoid analog **2** (73%), oil; ^{1}H nmr (300 MHz, deuteriochloroform): δ 8.05 (d, J = 8.5 Hz, 1H, naphthalene proton), 7.97 (d, J = 8 Hz, 1H, naphthalene proton), 7.9-7.87 (m, 1H, naphthalene proton), 7.58-7.45 (m, 4H, naphthalene protons), 7.12 (d, J = 1.5 Hz, 1H, phenyl proton), 6.75 (d, J = 1.5 Hz, 1H, phenyl proton), 5.85 (broad s, 1H, OH), 5.41 (d, J = 3.3 Hz, 1H, H_8), 3.29-3.26 (dd, J = 10 and 2 Hz, 1H, $H_{10\alpha}$), 2.78-2.7 (m, 1H, H_{10a}), 2.26-2.10 (m, 1H, H_7), 1.92-1.7 (m, 3H, $H_{6\alpha}$, H_7, $H_{10\beta}$), 1.67 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.06 (s, 3H, CH_3); ms: m/z 399 (M+1).

Anal. Calcd. for $C_{27}H_{26}O_3$: C, 81.37; H, 6 58. Found: C, 81.00; H, 6.74.

α-(1-Hydroxy-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-6*H*-dibenzo[*b*,*d*]pyran-3-yl)-α-(1-naphthyl)methanol (**3**).

Cannabinoid derivative **2**, (46 mg, 0.114 mmole) was dissolved in methanol (0.78 ml) and the mixture cooled to -10°. Sodium borohydride (8.8 mg, 0.23 mmole) was added in one

portion and stirring continued at -10° for 2 hours, whereupon the reaction was quenched by the addition of a saturated solution of ammonium chloride. The mixture was concentrated *in vacuo* to remove most of the methanol. The residue was extracted with ethyl acetate (3 x 5 ml), and the organic phase washed with water (5 ml), brine (5 ml), and dried over anhydrous sodium sulfate. Filtration, evaporation and purification by flash column chromatography (30% diethyl ether-petroleum ether as eluent) yielded 36 mg of cannabinoid analog **3** (78%); oil; ^{1}H nmr (300 MHz, deuteriochloroform): δ 8.03 (m, 1H, naphthalene proton), 7.87-7.78 (m, 2H, naphthalene protons), 7.69-7.66 (m, 1H, naphthalene proton), 7.5-7.42 (m, 3H, naphthalene protons), 6.5 (d, J = 1.3 Hz, 1H, phenyl proton), 6.36 (d, J = 1.3 Hz, 1H, phenyl proton), 6.29 and 6.26 (broad s, 0.5H each, C*H*OH), 5.4 (d, J = 3.2 Hz, 1H, H_8), 4.73 (broad s, 1H, OH), 3.18-3.13 (m, 1H, $H_{10\alpha}$), 2.77-2.66 (m, 1H, H_{10a}), 2.26-1.70 (m, 4H, $H_{6\alpha}$, H_7, $H_{10\beta}$), 1.68 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.07 (s, 3H, CH_3); ms: m/z 401 (M+1).

Anal. Calcd. for $C_{27}H_{28}O_3$: C, 80.96; H, 7.05. Found: C, 81.46; H, 7.31.

1,3-Dimethoxy-5-(1-naphthylmethyl)benzene (**9**).

To a refluxing solution **5**, (50 mg, 0.17 mmole) and triphenylphosphine (116.3 mg, 0.443 mmole) in dry toluene (0.85 ml), iodine was added (112.5 mg, 0.443 mmole). Heating was continued for 1 hour, then five drops of anhydrous ethanol was added. The mixture was allowed to cool to room temperature, decanted and the residue was washed with ethyl acetate (2 x 10 ml). The combined organic extracts were washed with a saturated solution of sodium thiosulfate (5 ml), water (5 ml), brine (5 ml), dried, filtered and the solvent was evaporated. Purification by flash column chromatography (10% diethyl ether-petroleum ether as eluent) provided 44 mg of **9** (94% yield), oil; ^{1}H nmr (300 MHz, deuteriochloroform): δ 7.99-7.97 (m, 1H, naphthalene proton), 7.85-7.83 (m, 1H, naphthalene proton), 7.81-7.72 (m, 1H, naphthalene proton), 7.45-7.40 (m, 3H, naphthalene protons), 7.39-7.26 (m, 1H, naphthalene proton), 6.36 (d, J = 1.8 Hz, 2H, phenyl protons), 6.30 (d, J = 1.8 Hz, 1H, phenyl proton), 4.36 (s, 2H, -CH_2-), 3.70 (s, 6H, OMe); ms: m/z 279 (M+1).

1,3-Dihydroxy-5-(1-naphthylmethyl)benzene (**10**).

Boron tribromide (0.26 ml, 2.7 mmoles) was added to a solution of 1,3-dimethoxy-5-(1-naphthylmethyl) benzene (**9**), (250 mg, 2.33 mmoles) in methylene chloride (22.5 ml) at -78° under an argon atmosphere. Following the addition of boron tribromide the reaction temperature was raised gradually over a period of 3 hours to 0°. Stirring was continued at that temperature until completion of the reaction (12 hours). Unreacted boron tribromide was destroyed by addition of methanol (3 ml). The methylene chloride was removed *in vacuo* and the residual oil was diluted with ethyl acetate (50 ml). The solution was washed with saturated sodium hydrogen carbonate (2 x 10 ml), water (2 x 10 ml) and brine (2 x 10 ml). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by flash column chromatography (40% diethyl ether-petroleum ether as eluent) gave 192 mg of compound **10** (85%), oil; ^{1}H nmr (300 MHz, deuteriochloroform): δ 8.06-7.91 (m, 1H, naphthalene proton), 7.90-7.88 (m, 1H, naphthalene proton), 7.82-7.79 (m, 1H, naphthalene proton), 7.47-7.37 (m, 4H, naphthalene protons), 6.20 (s, 3H, phenyl protons), 4.30 (s, 2H, -CH_2-), 2.05 (broad s, 1H, OH); ms: m/z 251 (M+1).

1-Naphthylmethyl Δ^8-Tetrahydrocannabinol (**4**).

This compound was prepared according to the method we followed for the preparation of the cannabinoid analog **1**, oil; ^{1}H nmr (300 MHz, deuteriochloroform): δ 7.99-7.96 (m, 1H, naphthalene proton), 7.85-7.82 (m, 1H, naphthalene proton), 7.76-7.73 (m, 1H, naphthalene proton), 7.45-7.30 (m, 4H, naphthalene protons), 6.33 (s, 1H, phenyl proton), 6.00 (s, 1H, phenyl proton), 5.41 (d, J = 3.2 Hz, 1H, H_8), 4.64 (s, 1H, OH), 4.26 (s, 2H, -CH_2-), 3.17 (dd, J = 10 and 2 Hz, 1H, $H_{10\alpha}$), 2.76-2.67 (m, 1H, H_{10a}), 2.21-2.09 (m, 1H, H_7), 1.85-1.70 (m, 3H, $H_{6\alpha}$, H_7, $H_{10\beta}$), 1.67 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.08 (s, 3H, CH_3); ms: m/z 385 (M+1).

Anal. Calcd. for $C_{27}H_{26}O_2$: C, 84.34; H, 7.34. Found: C, 84.84; H, 7.76.

Acknowledgment.

We thank the National Hellenic Research Foundation for their generous support of our programs and a research assistanship to T.K. We would like to express our gratitude to Dr. E. Kalatzis for providing us the elemental analyses and mass spectra data. The work was also supported by grants from NIDA, DA 3801 and DA 9158.

REFERENCES AND NOTES

[1] W. A. Devane, L. Hanus, A. Breuer, R. G. Pertwee, L. A. Stevenson, G. Griffin, D. Gibson, A. Mandelbaum, A. Etinger and R. Mechoulam, *Science*, **258**, 1946 (1992).

[2] W. A. Devane, F. A. Dysartz, M. R. Johnson, L. S. Melvin and A. C. Howlett, *Mol. Pharmacol.*, **34**, 605 (1988).

[3] S. Munro, K. L. Thomas, M. Abu-Shaar, *Nature*, **365**, 61 (1993).

[4] A. Makriyannis and R. S. Rapaka, *Life Sci.*, **47**, 2173 (1990).

[5] M. R. Johnson and L. S. Melvin, U. S. Patent 4,921,994 (1990); *Chem. Abstr.*, **114**, 74558g (1991).

[6] M. R. Bell, T. E. D'Ambra, V. Kumar, M. A. Eissenstat, J. L. Herrmann, J. R. Wetael, D. Rosi, R. E. Philion, S. J. Daum, D. J. Hlasta, R. K. Kullnig, J. H. Ackerman, D. R. Haubrich, D. A. Luttinger, E. R. Baizman, M. S. Miller and S. J. Ward, *J. Med. Chem.*, **34**, 1099 (1991).

[7] X. Xie, M. Eissenstat and A. Makriyannis, *Life Sci.*, **56**, 1963 (1995).

[8] C. A. Reece, J. O. Rodin, R. G. Brownlee, W. G. Duncan and R. M. Silverstein, *Tetrahedron*, **24**, 4249 (1968).

[9] F. Bohlmann, J. Sraffeldt and W. Skuballa, *Chem. Ber.*, **109**, 1586 (1976).

[10] D. R. Compton, K. C. Rice, B. R. De Costa, R. K. Razdan, L. S. Melvin, M. R. Johnson and B. R. Martin, *J. Pharmacol. Exp. Ther.*, **265**, 218 (1993).