SYNTHESIS OF [5,6-$^{13}C_2$, 1-^{14}C]OLIVETOLIC ACID, METHYL [1'-^{13}C]OLIVETOLATE AND [5,6-$^{13}C_2$, 1-^{14}C]CANNABIGEROLIC ACID

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SUMMARY

Potential advanced intermediates in the biosynthesis of Δ^9-tetrahydrocannabinol have been synthesized labeled with two contiguous ^{13}C atoms and ^{14}C. Methyl [5,6-$^{13}C_2$, 1-^{14}C]olivetolate was prepared from lithium [$^{13}C_2$]acetylide and dimethyl [2-^{14}C]malonate. Reaction with geranyl bromide afforded methyl [5,6-$^{13}C_2$, 1-^{14}C]cannabigerolate, and hydrolysis of these methyl esters with lithium propyl mercaptide yielded the corresponding labeled acids. The ^{13}C-^{13}C couplings observable in the ^{13}C NMR spectra of these ^{13}C-enriched compounds and their synthetic precursors are recorded. Methyl [1'-^{14}C]olivetolate was prepared from $^{13}CO_2$ to confirm assignments of the ^{13}C chemical shifts in the pentyl side chain of these compounds.

Key Words: Carbon-13, Carbon-14, Olivetolic acid, Cannabigerolic acid, ^{13}C NMR, ^{13}C-^{13}C Couplings.

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INTRODUCTION

Very little definitive work (1-3) has been carried out on the biosynthesis of Δ^9-tetrahydrocannabinol (**4**), the major psychoactive principle of marijuana (Cannabis sativa). Figure 1 is an abbreviated version of the various biogenetic schemes which have been suggested (4-7) for the origin of **4**. The

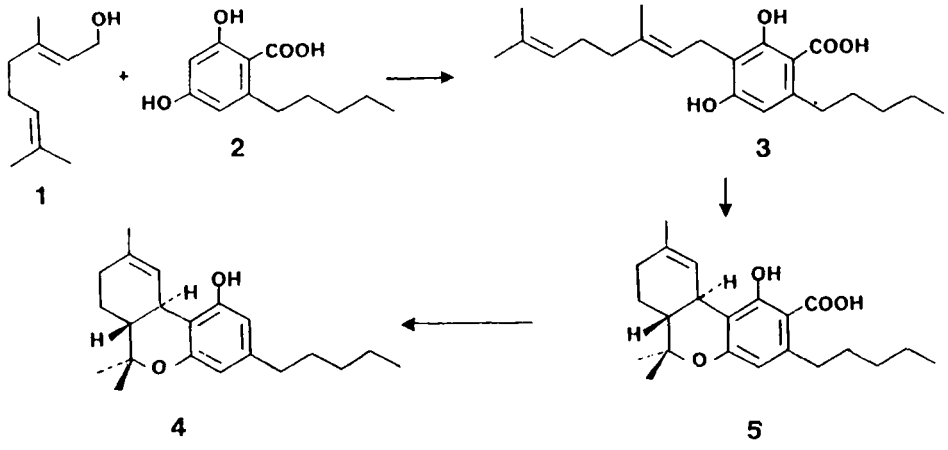

FIGURE 1. Biogenesis of Δ^9-Tetrahydrocannabinol.

primary precursors of the cannabinoids are considered to be geraniol (**1**) and olivetolic acid (**2**), the latter being a polyketide derived from six acetate units. A plausible condensation between geraniol pyrophosphate and **2** affords cannabigerolic acid (**3**). A cyclization, via unknown intermediates, affords Δ^9-tetrahydrocannabinolic acid A (**5**) which then underoges decarboxylation to yield **4**. It has also been proposed (3) that **4** could be formed by a more direct route involving geraniol and olivetol (**2**, lacking the COOH). To investigate this biogenetic hypothesis our plan is to administer to Cannabis these potential

precursors of **4**, labeled with two contiguous ^{13}C atoms, so that their direct incorporation can be monitored by ^{13}C NMR spectroscopy (8-10). Carbon-14 was also introduced into these molecules so that the degree of incorporation can be readily determined by radioactive assay.

RESULTS AND DISCUSSION

Figure 2 illustrates the synthesis of **2** and **3** using a combination of various literature procedures modified so that the desired isotopes could be incorporated in high yield. The stable ethylene diamine complex of lithium

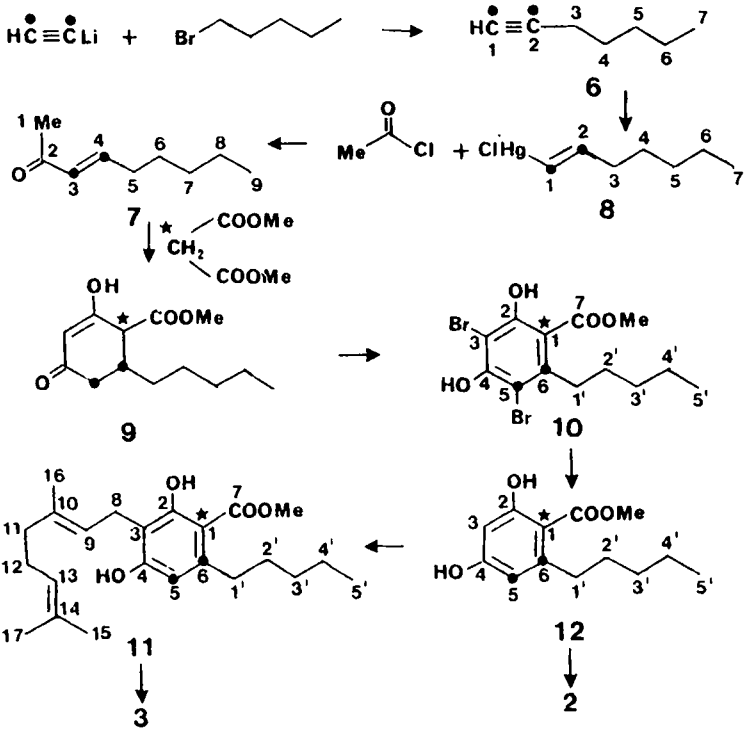

FIGURE 2. Synthesis of [5,6-$^{13}C_2$, 1-^{14}C]Olivetolic and Cannabigerolic Acids (• ^{13}C, ★ ^{14}C).

[$^{13}C_2$]acetylide reacted with 1-bromopentane in dimethyl sulfoxide to yield [1,2-$^{13}C_2$]-1-heptyne **6** (11). Reaction of this alkyne with catechol borane afforded a dioxaborole which was converted to [1,2-$^{13}C_2$]-(E)-1-heptenylmercuric chloride, **8**, by treatment with mercuric acetate followed by sodium chloride (12,13). Reaction of this mercuric compound with acetyl chloride in the presence of aluminum chloride yielded (E)-3-nonen-2-one, **7** (14). Reaction of this ketone with dimethyl [2-^{14}C]malonate in the presence of sodium methoxide afforded the cyclohexenone **9** which on bromination yielded methyl [5,6-$^{13}C_2$, 1-^{14}C]-3,5-dibromo-2,4-dihydroxy-6-pentylbenzoate, **10** (15,16). Debromination was carried out with Raney nickel alloy dissolving in aqueous sodium hydroxide (17) to afford methyl [5,6-$^{13}C_2$, 1-^{14}C]olivetolate, **12**. This ester was cleaved with lithium propyl mercaptide (18, 19) to afford [5,6-$^{13}C_2$, 1-^{14}C]olivetolic acid, **2**. Reaction of the methyl olivetolate with butyl lithium followed by geranyl bromide yielded methyl [5,6-$^{13}C_2$, 1-^{14}C]cannabigerolate **11**, (20), which was hydrolysed as before to the free acid **3**.

The ^{13}C NMR spectra of these compounds are recorded in Table I. Because of the presence of the two highly enriched positions (> 99% ^{13}C) short and long range ^{13}C-^{13}C coupling were readily observed and are also recorded. Several papers have appeared on the ^{13}C NMR spectra of the cannabinoids (21-25). One problem is the assignment of C-2' and C-3' of the pentyl side chains. These carbons have chemical shifts which are very close together (only 0.3 ppm different in pentylbenzene). Assignments were made (23) in this compound by the preparation of [2'-$^2H_2$]pentylbenzene and C-2' was assigned upfield of C-3'. However in an earlier study (21) on 1,3-dimethoxy-5-pentylbenzene the assignment of these equivalent carbons was reversed. In order to unequivocally assign the signals for C-2' and C-3', methyl olivetolate was prepared in which the benzylic carbon was enriched with ^{13}C. In this compound, and its synthetic precursors which contain a pentyl side chain, the methylene group at C-2' adjacent to the highly enriched C-1' position will be observed as a doublet in its ^{13}C NMR spectrum, these signals being due to spin-spin coupling of the contiguous ^{13}C atoms, typically 33-34 Hz for two sp^3 carbons. The ^{13}C NMR spectra of these

compounds are recorded in Table II and it is observed that C-2' is always upfield of C-3', thus confirming the previous assignments in the cannabinoids (23). The synthesis of these olivetol derivatives is illustrated in Figure 3.

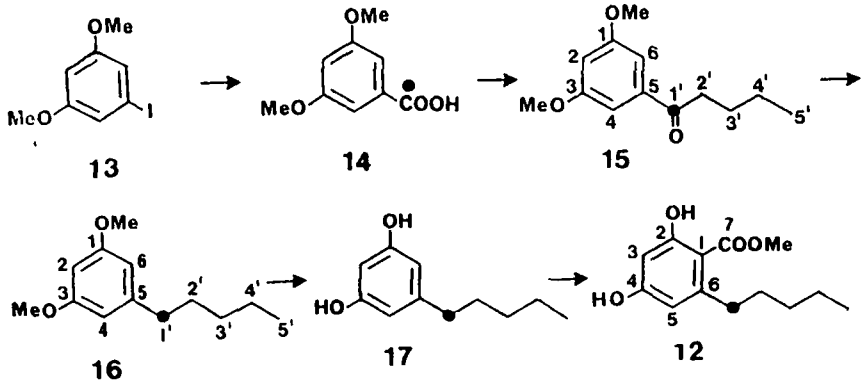

FIGURE 3. Synthesis of Methyl[1'-^{13}C]olivetolate (• ^{13}C).

The aryl lithium formed from 3,5-dimethoxyiodobenzene **13** by reaction with tert-butyl lithium was carboxylated with $^{13}CO_2$ to yield [carboxy-^{13}C]-3,5-dimethoxybenzoic acid **14**. Reaction of this acid with two equivalents of n-butyl lithium afforded 3,5-dimethoxyphenyl-1-pentanone **15**. Reduction of this ketone with hydrogen in the presence of palladium on charcoal yielded 1,3-dimethoxy-5-pentylbenzene **16** (26). Refluxing with 48% hydrobromic acid yielded olivetol **17** which was carboxylated with methyl magnesium carbonate in dimethylformamide (18). Treatment of the resultant olivetolic acid with diazomethane yielded methyl [1'-^{13}C]olivetolate **12**.

Table I. Carbon Shifts of [5,6-$^{13}C_2$]Olivetolic Acid, Cannabigerolic Acid and their Synthetic Precursors

Compound	2[a]	3[a]	6	7	8	10	11	12
Carbon #								
1	104.2 ($^1J_{1,6}$ 60.9)	103.2[b]	67.9 ($^1J_{1,2}$ 170.5)	26.8 ($^2J_{1,3}$ 15.2)	132.8 ($^1J_{1,2}$ 66.0) ($^1J_{1,Hg^{2230}}$)	107.1 ($^1J_{1,6}$ 66.0) ($^2J_{1,5}$ 3.3)	104.6[b]	104.9 ($^1J_{1,6}$ 62.0)
2	167.2	163.7 ($^3J_{2,5}$ 6.0)	84.7 ($^1J_{1,2}$ 170.5)	198.5 ($^1J_{2,3}$ 55.6)	151.0 ($^1J_{1,2}$ 66.0) ($^2J_{2,Hg}$ 36.0)	159.7 ($^3J_{2,5}$ 4.6)	162.7 ($^3J_{2,5}$ 6.5)	164.9 ($^2J_{2,6}$ 2.7) ($^3J_{2,5}$ 4.7)
3	101.6	111.9	18.2 ($^1J_{2,3}$ 63.3) ($^2J_{1,3}$ 12.5)	131.3 ($^1J_{3,4}$ 68.1)	36.2 ($^1J_{2,3}$ 38.7)	96.6 ($^2J_{3,5}$ 3.4) ($^3J_{3,6}$ 7.5)	111.9[b]	101.5
4	163.4 ($^1J_{4,5}$ 63.1)	160.6 ($^1J_{4,5}$ 66.7)	28.1 ($^2J_{2,4}$ 1.9) ($^3J_{1,4}$ 3.1)	148.5 ($^1J_{3,4}$ 68.1)	28.4 ($^3J_{1,4}$ 4.2)	154.1 ($^1J_{4,5}$ 71.7) ($^2J_{4,6}$ 2.8)	159.6 ($^1J_{4,5}$ 64.9)	160.9 ($^1J_{4,5}$ 62.7)
5	111.5 ($^1J_{5,6}$ 60.6)	111.3 ($^1J_{5,6}$ 61.4)	30.8 ($^3J_{2,5}$ 3.7)	32.5 ($^1J_{4,5}$ 40.5)	31.3 ($^3J_{2,5}$ 4.1)	105.2 ($^1J_{5,6}$ 69.2)	110.9 ($^1J_{5,6}$ 61.4)	111.2 ($^1J_{5,6}$ 60.8)
6	149.8 ($^1J_{5,6}$ 60.6)	147.6 ($^1J_{5,6}$ 61.4)	22.0	27.9 ($^3J_{3,6}$ 5.4)	22.4	145.1 ($^1J_{5,6}$ 69.2)	145.7 ($^1J_{5,6}$ 61.4)	149.2 ($^1J_{5,6}$ 60.8)
7	174.0 ($^3J_{5,7}$ 3.6)	176.4	13.9	31.4 ($^3J_{4,7}$ 2.7)	14.0	171.1 ($^2J_{6,7}$ 2.8) ($^3J_{5,7}$ 6.9)	172.2	172.2 ($^2J_{6,7}$ 2.6) ($^3J_{5,7}$ 5.5)

8			22.5			
9			13.9			
1'	37.0 ($^1J_{1',6}$ 41.4) ($^2J_{1',5}$ 2.5)	36.5 ($^1J_{1,6}$ 41.5)		35.8 ($^1J_{1',6}$ 43.2)	36.8 ($^1J_{1',6}$ 42.7) ($^2J_{1,5}$ 2.6)	36.8 ($^1J_{1',6}$ 42.9) ($^2J_{1',5}$ 2.4)
2'	32.2	31.4		29.1	31.6	31.5
3'	32.6 ($^3J_{3',6}$ 3.7)	32.0 ($^3J_{3',6}$ 3.9)		32.1 ($^3J_{3',6}$ 4.2)	32.2 ($^3J_{3',6}$ 3.9)	32.2 ($^3J_{3',6}$ 3.9)
4'	22.9	22.5		22.3	22.6	22.5
5'	14.1	14.0		14.1	14.0	14.1
OMe				52.8	51.7	52.0

The carbons of the geranyl side chain of compounds **3** and **11** were as follows:

Carbon #: -	8	9	10	11	12	13	14	15	16	17
3	22.1	121.4	139.0	39.7	26.4	23.9	132.9	25.6	16.2	17.6
11	22.1	121.7	138.6	39.8	26.5	124.0	131.8	25.7	16.2	17.7

Spectra are recorded in ppm, downfield from Me_4Si, and were determined in $CDCl_3$, unless otherwise stated. Coupling constants (J) are recorded (in Hz) below the signals where they were observed. [a]Determined in acetone-d_6. [b]This is the chemical shift for unenriched material, the signal being obscured by the resonance due to the highly enriched C-5.

Table II. Carbon Shifts of Methyl [1'-^{13}C]Olivetolate and Related Compounds

Compound	**15**[a]	**16**	**17**	**12**
Carbon #				
1	161.5 ($^3J_{1,1'}$ 5.5)	160.8	156.3 ($^3J_{1,1'}$ 5.3)	104.9
2	105.2	97.2	100.6	164.9
3	161.2 ($^3J_{3,1'}$ 5.5)	160.8 ($^3J_{3,1'}$ 5.3)	156.3 ($^3J_{1',3}$ 5.3)	101.5
4	106.1	106.6 ($^2J_{1',4}$ 1.7)	108.6	160.9 ($^3J_{1',4}$ 4.3)
5	139.4 ($^1J_{1',5}$ 62.1)	145.4 ($^1J_{1',5}$ 42.7)	146.7 ($^1J_{1',5}$ 42.8)	111.2
6	106.1	106.6	108.6 ($^2J_{1',6}$ 1.7)	149.2 ($^1J_{1',6}$ 42.4)
7				172.2
1'	200.2	36.3	35.9	36.8
2'	38.6 ($^1J_{1',2'}$ 41.7)	30.9 ($^1J_{1',2'}$ 34.3)	30.7 ($^1J_{1',2'}$ 33.3)	31.5 ($^1J_{1',2'}$ 33.4)
3'	26.8	31.4	31.7	32.1
4'	22.7 ($^3J_{1',4'}$ 1.7)	22.6 ($^3J_{1',4'}$ 3.0)	22.7	22.5 ($^3J_{1',4'}$ 3.3)
5'	14.1	14.0	14.1	14.0
OMe	55.7 ($^5J_{1',OMe}$ 2.3)			52.0

Spectra are recorded in ppm, downfield from Me_4Si, in $CDCl_3$. Coupling constants (J) are recorded (in Hz) below the signals where they were observed. [a]This compound (**15**) is numbered in this unconventional way to facilitate comparison with the other compounds in this Table.

EXPERIMENTAL

Melting points are uncorrected. Elemental analyses were determined by M-H-W Laboratories, Phoenix, Arizona. High performance liquid chromatography (HPLC) was carried out in a Waters Associates instrument, Model ALC-GPL-244 under isocratic conditions. The ^{13}C NMR spectra were determined on a Varian XL-100-15 spectrometer operating at 25.2 MHz in the Fourier transform mode.

[1,2-$^{13}C_2$]-1-Heptyne (**6**). The ethylene diamine complex of lithium [$^{13}C_2$]acetylide (2.00 g, 93% pure, 99.3% $^{13}C_2$ 19.8 mmol) was stirred in dimethyl sulfoxide (11 mL) in an argon atmosphere at 0°C. 1-Bromopentane (3.0 g, 19.9 mmol) was slowly added with a syringe during one hr, and the stirring continued for an additional 2 hr. Water (5 mL) was then added and the reaction mixture distilled at 105°C into a Dean-Stark trap. The trap was washed out with pentane. Subsequent fractional distillation afforded 1-heptyne, bp 100°C (1.42 g, 73%).

[1,2-$^{13}C_2$]-(E)-1-Heptenylmercuric Chloride (**8**). Freshly distilled catechol borane (1.93 mL) was added with a syringe to the 1-heptyne (1.41 g, 14.4 mmol) in an argon atmosphere at 20°C. The reaction mixture was then stirred at 70°C for 1.5 hr. Distillation (100°C, 0.1 mm) afforded 4,5-benzo-2-heptenyl-1,3,2-dioxaborole (1.81 g). Mercuric acetate (2.63 g, 8.26 mmol) was added to a solution of this dioxaborole (1.81 g, 8.30 mmol) in THF (8.5 mL) at 0°C. After 10 min all the mercuric acetate had dissolved and the reaction mixture was added to a solution of NaCl (486 mg, 8.31 mmol) in water (25 mL) at 0°C. After 10 min the organic layer was separated. The aqueous layer was extracted with diethyl ether (3 x 25 mL). The combined organic layers were evaporated under reduced pressure and the residue subjected to column chromatography on silica gel (100 g). Elution with a mixture of hexane and ethyl acetate (19 : 1) afforded **8** (2.61 g, 54%). An analytical sample was further purified by crystallization from 95% EtOH, affording colorless plates, mp 113-114°C. Anal. Calcd. for $C_7H_{13}ClHg$ (unenriched): C, 25.23; H, 3.93; Cl, 10.64. Found: C, 25.13; H, 3.99; Cl, 10.43%.

[3,4-$^{13}C_2$]-(E)-3-Nonene-2-one (**7**). Acetyl chloride (570 mg, 7.26 mmol) was added to a stirred suspension of aluminum chloride (1.0 g, 7.50 mmol) in methylene chloride (50 mL) at 20°C. The heptenyl mercuric chloride (2.40 g, 7.16 mmol) in methylene chloride (5 mL) was added all at once to the reaction mixture when a white precipitate separated. After 10 min the mixture was added to water (50 mL). The water layer was extracted with methylene chloride (2 x 60 mL). The combined organic layers were concentrated to 50 mL and washed with 5% $NaHCO_3$, and 3M sodium thiosulfate. The residue obtained on evaporation of the dried (Na_2SO_4) extract was distilled (80°C, 0.1 mm) to afford **7** as a colorless liquid (896 mg, 88%).

Methyl [5,6-$^{13}C_2$, 1-^{14}C]-3,5-Dibromo-2,4-dihydroxy-6-pentylbenzene (**10**). Diethyl [2-^{14}C]malonate (8.0 mg, nominal activity 0.25 mCi) was mixed with dimethyl malonate (1.20 g) and added to a solution of sodium (183 mg, 8.0 mg-atom) in methanol (8 mL). After stirring at 50°C for 1 hr, the 3-nonen-2-one, **7** (896 mg, 6.30 mmol) was added slowly during 0.5 hr, and the reaction mixture then refluxed for 5 hr. The residue obtained on evaporation of the methanol solution was dissolved in 1 N NaOH (30 mL) which was washed with chloroform (3 x 30 mL). The aqueous layer was adjusted to pH 4 with HCl and extracted with chloroform (3 x 30 mL). The dried (Na_2SO_4) extract was evaporated to afford the cyclohexenone **9** (1.35 g). Bromine (2.78 g) in acetic acid (3 mL) was added slowly to a solution of the ketone **9** (1.35 g) in acetic acid (4.5 mL) at 20°C stirred in a nitrogen atmosphere. After 3 hr the reaction mixture was added to water (50 mL) at 0°C. The mixture was extracted with diethyl ether, which was then dried ($MgSO_4$) and evaporated to yield crude **10** (2.36 g). A sample crystallized from benzene-hexane had mp 61-62°C, lit (**17**) mp 63-64°C.

Methyl [5,6-$^{13}C_2$, 1-^{14}C]Olivetolate (**12**). Raney nickel alloy (2.2 g) was added in small portions during 30 min to a stirred solution of the crude dibromo compound **10** (2.35 g) in 2 N NaOH (48 mL) cooled to 0°C. After stirring for an additional 30 min the solution was added to N HCl (100 mL) and the mixture extracted with diethyl ether (3 x 150 mL). The residue obtained on

evaporation of the dried ($MgSO_4$) extract was subjected to column chromatography on silica gel. Elution with diethyl ether-hexane (1 : 2) yielded **12** which crystallized from ethyl acetate as colorless prisms (1.11 g, 78%) mp 77-78°C, lit (27) mp 78°C, having a specific activity of 7.92×10^7 dpm/mmol. This activity is higher than the theoretical (6.04×10^7) presumably due to the generosity of the supplier of the [2-^{14}C]malonate (Amersham).

[5,6-$^{13}C_2$, 1-^{14}C]Olivetolic Acid (**2**). The labeled methyl olivetolate (502 mg, 2.1 mmol) was added to a solution of lithium propyl mercaptide (19) (6 mL of a 0.5 M solution in hexamethylphosphoramide) and the mixture stirred at 20°C for 2.5 hr under an argon atmosphere. The reaction mixture was then added to N HCl (300 mL) and the solution extracted with diethyl ether (3 x 200 mL). The ether extract was concentrated to 50 mL and extracted with 2 N NaOH (3 x 50 mL). This solution was then adjusted to pH 2 with HCl and extracted with diethyl ether (3 x 100 mL). The residue obtained on evaporation of the dried (Na_2SO_4) extract was crystallized from benzene affording colorless needles of **2**, mp 141-142°C, lit (27) mp 142°C, having a specific activity of 7.88×10^7 dpm/mmol. The mother liquor from the initial crystallization was subjected to preparative TLC on silica gel PF-254 (Merck) developing with a mixture of hexane, diethyl ether, acetic acid (66 : 33 : 1). The acid **2** had an R_f of 0.5 and was extracted from the silica gel with diethyl ether. The combined yield was 402 mg (85%).

Methyl [5,6-$^{13}C_2$, 1-^{14}C]Cannabigerolate (**11**). n-Butyl lithium (1.04 mL of a 2.05 M solution in hexane, 2.13 mmol) was added to a stirred solution of the labeled methyl olivetolate (500 mg, 2.08 mmol) in benzene (25 mL) at 20°C in an argon atmosphere. After one hr a solution of geranyl bromide (28) (506 mg, 2.33 mmol) in benzene (2 mL) was added and the mixture refluxed for 4 hr. Water (30 mL) was added to the cooled reaction mixture and the pH of the aqueous layer adjusted to pH 4 with HCl. The mixture was extracted with diethyl ether (3 x 25 mL). The residue obtained on evaporation of the dried (Na_2SO_4) extract was subjected to column chromatography on silica gel. The ester **11** (340 mg, 43%) was eluted with a mixture of hexane and diethyl ether (19 : 1).

[5,6-$^{13}C_2$, -1-^{14}C]Cannabigerolic Acid (3). The methyl ester **11** (337 mg) was hydrolysed with lithium propylmercpatide as described for olivetolic acid. Final purification was carried out by HPLC on silica gel eluting with a mixture of hexane, THF, and acetic acid (92 : 7 : 1). It was obtained as a crystalline solid, (94.3 mg, 26%) mp 108-110°C. This compound was previously described as an oil (29).

[carboxy-^{13}C]-3,5-Dimethoxybenzoic Acid (**14**) tert-Butyl lithium (13.9 ml, 1.4 M in pentane, 19.5 mmol) was added to a solution of 3,5-dimethoxyiodobenzene (30) (2.55 g, 9.65 mmol) in THF (50 mL) at -70°C in an argon atmosphere. The reaction mixture was then frozen in a bath of liquid nitrogen and [^{13}C]carbon dioxide, generated by the action of concentrated sulfuric acid (60 mL) on barium [^{13}C]carbonate (2.25 g, 91.7% ^{13}C, 11.3 mmol), passed into the reaction vessel which was then allowed to warm to -75°C. After stirring for 1 hr, water (40 mL) was added to the reaction mixture. The organic layer was extracted with 5% $NaHCO_3$ (3 x 40 mL) and the combined aqueous layers acidified with HCl yielding the [carboxyl-^{13}C]-3,5-dimethoxybenzoic acid as a white solid (0.97 g 55%) mp 180-182°C, lit (31) mp 182-184°C.

3,5-Dimethoxyphenyl-[1'-^{13}C]-1-pentanone (**15**) n-Butyl lithium (4.86 mL of a 2.4 M solution in hexane, 11.7 mmol) was added during 45 min to a solution of the ^{13}C-labeled **14** (0.97 g, 5.32 mmol) in THF (15 mL) at 0°C in an argon atmosphere. After stirring for an additional 30 min, water (25 mL) and diethyl ether (50 mL) were added. The organic layer was washed with saturated aqueous NaCl and dried over $MgSO_4$. Evaporation of the solvent afforded crude **15** (1.17 g, 98%) some of which was crystallized from 95% EtOH affording colorless needles, mp 39-41°C, lit (32) mp 42-43°C.

[1'-^{13}C]-1,3-Dimethoxy-5-pentylbenzene (**16**). The ketone **15** (1.06 g, 4.76 mmol) dissolved in methanol (40 mL) was hydrogenated in the presence of 20% palladium on charcoal (124 mg) at 3 atmospheres pressure for 3 hr. Evaporation of the filtered reaction mixture afforded **16** as a colorless oil, which was purified by column chromatography on silica gel, developing with a mixture of diethyl ether and hexane (424 mg, 43%).

[1'-^{13}C]-1,3-Dihydroxy-5-pentylbenzene, [1'-^{13}C]Olivetol (17). Dimethylolivetol (16) (409 mg, 1.95 mmol) was refluxed with 48% HBr (10 mL) in an argon atmosphere for 6 hr. After diluting with water (20 mL) the mixture was extracted with methylene chloride. The residue obtained on evaporation of the dried (Na_2SO_4) extract was subjected to TLC on silica gel PF-254, developing with a mixture of diethyl ether and hexane (1 : 2). Ether extraction of the zone (R_f 0.1) yielded olivetol, purified by distillation (155°C, 0.1 mm) (334 mg, 94%).

Methyl [1'-^{13}C]Olivetolate (12). Olivetol (17) (330 mg, 1.82 mmol) was added to a solution of methyl magnesium carbonate (33) (1.23 g, 9.4 mmol) in dimiethylformamide (4 mL) and the mixture stirred at 118°C in an argon atmosphere for 3 hr. 3 N HCl (20 mL) was added to the cooled reaction mixture, which was then extracted with diethyl ether (3 x 20 mL). The residue obtained on evaporation of this extract was dissolved in 5% $NaHCO_3$ which was washed with methylene chloride. The aqueous solution was adjusted to pH 2 with HCl and extracted with diethyl ether. An ether solution of diazomethane was added until a persistent yellow color remained. The residue obtained on evaporation of this ether solution was subjected to TLC on silica gel PF-254, developing with a mixture of diethyl ether and hexane (1 : 2). An ether extract of the zone R_f = 0.5 afforded methyl olivetolate as colorless needles (from hexane) mp 77-78°C, lit (27) mp 78°C.

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