extracted with ether. The ethereal extracts were combined, washed with water, and dried over sodium sulfate. A thin-layer chromatogram (Kieselgel G, benzene/CH_2Cl_2, 2/1) confirmed the presence of only two components, benzophenone and benzhydrol. These materials were separated by column chromatography (Al_2O_3) by eluting with cyclohexane (100 mL), carbon tetrachloride (250 mL), benzene (250 mL), and chloroform (300 mL). The appropriate fractions were combined, and the products were recrystallized twice from petroleum ether (80–90 °C). Samples (50-mg) of each of the materials were dissolved in the scintillation solution and the time required for 10^4 impulses was measured. From the time values obtained for each sample, the amount of active benzophenone and/or benzhydrol per 50-mg sample was determined by comparison to previously prepared calibration curves. In all cases, over 95% of the radioactivity could be accounted for. No exchange of carbon-14 was observed under the conditions of chromatographic separation. Three kinetic runs were made in which the reaction was followed through ca. 2 half-lives. These data are presented in Table I.

The rate of carbon-14 exchange, R, for a reaction of the type

$$BX^* + AX \rightleftharpoons AX^* + BX$$

is given by the general expression:[15]

$$R = -\frac{ab}{a+b}\left\{\frac{2.3}{t}\log\left[1-(x/x_\infty)\right]\right\}$$

where a and b = total concentration of AX and BX*, respectively; X = concentration of active AX at time t; and $x_\infty = x$ at t_∞. Under the assumption that the reaction is second order, $K_2 = R/ab = -[2.3/a + b)t]\log[1 - (x/x_\infty)]$.[6e,16] A plot of log $[1 - (x/x_\infty)]$ vs. time was constructed and fitted by the method of least squares (correlation coefficient = 0.987). From the slope, R (and K_2) were evaluated.

Acknowledgment. R. D. H. gratefully acknowledges the support of an NSF Postdoctoral Fellowship, and the helpful discussions with Drs. A. Krebs, M. Rings, P. Suchanek, G. Steinhof, and H. Wulff during the course of this work.

Registry No.—Benzoic acid-*1*-^{14}C, 1589-66-8; benzophenone-*1*-^{14}C, 51594-23-1; benzyhydrol, 91-01-0; lithium benzhydrolate, 2036-66-0; benzhydrol-*1*-^{14}C, 55366-57-9.

References and Notes

(1) NSF Postdoctoral Fellowship Participant, Organisch Chemisches Institut, Heidelberg, W. Germany, 1964–1965.
(2) G. Wittig and H. D. Frommeld, *Chem. Ber.*, **97**, 3541 (1964).
(3) G. Wittig, H. F. Ebel, and G. Häusler, *Justus Liebigs Ann. Chem.*, **743**, 120 (1970).
(4) For a review of the role of ate complexes in organic chemistry, see W. Tochtermann, *Angew. Chem., Int. Ed. Engl.*, **5**, 351 (1966).
(5) G. E. Dunn and J. Warkentin, *Can. J. Chem.*, **34**, 75 (1956).
(6) (a) H. Meerwein, *J. Prakt. Chem.*, **147**, 211 (1936); (b) R. B. Woodward, N. L. Wendler, and F. J. Brutschy, *J. Am. Chem. Soc.*, **67**, 1425 (1945); (c) V. J. Shiner, Jr., and D. Whittaker, *ibid.*, **85**, 2337 (1963); (d) B. J. Yager and C. K. Hancock, *J. Org. Chem.*, **30**, 1174 (1965); (e) V. J. Shiner, Jr., and D. Whittaker, *J. Am. Chem. Soc.*, **91**, 394 (1969); (f) V. Hach, *J. Org. Chem.*, **38**, 293 (1973).
(7) W. v. E. Doering and T. C. Aschner, *J. Am. Chem. Soc.*, **75**, 393 (1953).
(8) A. Schonberg and A. Mustafa, *J. Chem. Soc.*, 276 (1943).
(9) G. A. Russell, E. G. Janzen, and E. T. Strom, *J. Am. Chem. Soc.*, **84**, 4155 (1962); **86**, 1807 (1964).
(10) R. B. Duffield and M. Calvin, *J. Am. Chem. Soc.*, **68**, 557 (1946).
(11) W. N. Moulton, R. E. Van Atta, and R. R. Ruch, *J. Org. Chem.*, **26**, 290 (1961).
(12) M. S. Bains and D. C. Bradley, *Chem. Ind. (London)*, 1032 (1961).
(13) A. Murray and D. I. Williams, "Organic Synthesis with Isotopes", Part I, Interscience, New York, N.Y., 1958, p 662.
(14) A. Murray and D. I. Williams, ref 13, p 524.
(15) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism", 2nd ed, Wiley, New York, N.Y., 1961, p 192.
(16) A. A. Frost and R. G. Pearson, ref 15, p 187.

A Simple and Practical Synthesis of Olivetol

Antonino Focella,* Sidney Teitel, and Arnold Brossi

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

Received March 7, 1977

The complete structural elucidation[1,2] of some psychotomimetically active components of marihuana and the extensive biological activity[3] of these components have stimulated interest in the synthesis of cannabinoids.[4–7] The synthesis of these compounds depends largely on the availability of the key intermediate olivetol, 1-*n*-pentyl-3,5-dihydroxybenzene, and homologs. A practical and efficient synthesis which makes these compounds readily available in quantity will considerably facilitate and stimulate further investigation of the synthetic and biological aspects of the cannabinoids.

While several papers on the synthesis of olivetol have appeared recently,[8–10] they did not differ much from the earlier investigations[11,12] in that 3,5-dimethoxybenzoic acid was used as the starting material. This substance is, in fact, expensive and not readily available. In the case where trimethoxy derivatives have been employed,[13] the in situ 4-demethoxylation, as Birch and Slabbe[9] pointed out, results in a poorer quality product. Finally, a recently described synthesis starting from an α,β-unsaturated ester[14] involves complicated steps and has severe steric limitations.

We would like to report a three-step total synthesis[15] of olivetol (**3**) from readily available aliphatic precursors. The α,β-unsaturated ketone[16] **1** was reacted with dimethyl malonate enolate to give the cyclic Michael adduct **2** which was aromatized and subsequently decarbomethoxylated when treated with bromine in DMF, initially at 0 °C[17] and then at refluxing temperature, to yield olivetol in 62% overall yield.

Alternatively, **2** was decarbomethoxylated by successive treatment with alkali and acid to afford the enol **4** which was etherified with methanolic hydrogen bromide to furnish the keto enol ether **5**. Aromatization with etherification[18] of **5** with cupric bromide in methanol gave 1-*n*-pentyl-3,5-dimethoxybenzene (**6**) in an overall yield of 37%. Compound **6** was then demethylated with pyridine hydrochloride to provide 82% of **3**.

Olivetol (**3**) prepared directly by route **1** → **2** → **3** (see Scheme I) is practical and inexpensive. This synthesis is general and suitable for the preparation of homologues of olivetol containing lower or higher or branched alkyl groups (see Table I). This sequence has also been used to incorporate a labeled carbon atom in the aromatic ring.[19]

The alternative route leads to a variety of intermediates which per se could be of synthetic interest. The keto-enol **4**, used originally by adams[20] and co-workers in the synthesis of cannabinol, was laboriously prepared by partial reduction of olivetol.

Experimental Section

All melting points (uncorrected) were taken in open capillary tubes in a Thomas–Hoover melting point apparatus. Vapor phase chromatographs were determined with an F & M Model 810 instrument, using a 4 ft × ¼ in. S.S. column of 3% silicon rubber on Diatoport 5 at 160 °C under helium gas flow of 90 mL/min. Infrared spectra were determined with a Beckman IR-5 infrared spectrophotometer and ultraviolet spectra were measured with a Cary Model 14 M spectro-

Scheme I

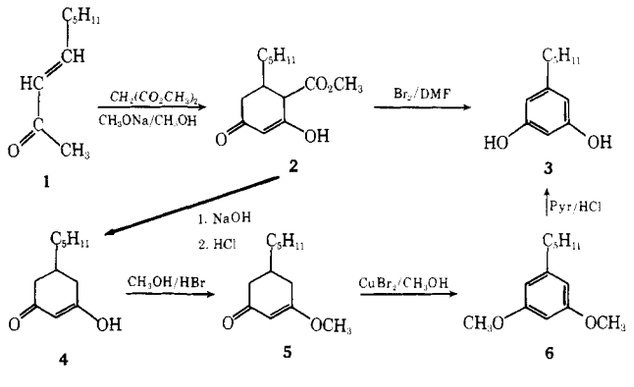

Table I. Other 1-Alkyl-3,5-dihydroxybenzene Prepared by the Direct Route

1 Substituent	Registry no.	Yield, %	Mp or bp, °C
Propyl	500-49-2	80.4	48–50 (lit.[21] mp 51)
Heptyl	500-67-4	74.7	55–56 (lit.[12] mp 55–55.5)
1-Methylheptyl	27871-95-0	86.4	Bp 129–130 (0.04 mm) (lit.[11] bp 179–184 (4 mm)

photometer. Nuclear magnetic resonance spectra were obtained with a Varian A-60A or HA-100 spectrometer.

Methyl 6-*n*-Pentyl-2-hydroxy-4-oxo-cyclohex-2-ene-1-carboxylate (2).[22] To a solution of 32.4 g (0.60 mol) of sodium methoxide and 90 g (0.68 mol) of dimethyl malonate in 230 mL of anhydrous methanol was added portionwise with stirring 75 g (0.48 mol) of 90% pure 3-nonen-2-one[16] (1). The reaction mixture was then refluxed for 3 h under N_2 and allowed to cool to room temperature. The solvent was distilled under reduced pressure and the residue dissolved in 350 mL of water. The slurry of white crystals and the almost clear solution was extracted with 3 × 80 mL of $CHCl_3$, the aqueous acidified to pH 4 with concentrated HCl and the white precipitate allowed to stand overnight and filtered. The crystals were dried at 50 °C under high vacuum for 5 h to yield 106.5 g (92%) of **2**, mp 96–98 °C. An analytical sample prepared from heptane gave mp 98–100 °C; IR ($CHCl_3$): 3180, 3270–2500 (OH), 1740, 1710 (C=O ester), 1600 cm^{-1} (C=O and C=C); NMR ($CDCl_3$): δ 0.90 (CH_3), 1.33 ($4CH_2$), 5.50 (−CH=), 9.23 (OH).

Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.01; H, 8.40.

1-*n*-Pentyl-3,5-dihydroxybenzene, Olivetol (3).[22] To an ice-cooled solution of 58.4 g (0.245 mol) of **2** dissolved in 115 mL of dimethylformamide was added dropwise with stirring a solution of 37.9 g (0.23 mol) of bromine dissolved in 60 mL of dimethylformamide. At the end of the addition (ca. 90 min) the reaction mixture was slowly heated to 80 °C during which time the evolution of carbon dioxide became quite vigorous. The reaction was maintained at this temperature until the gas evolution had ceased and was then heated to 160 °C and held at this temperature for 10 h. The DMF was removed under reduced pressure and the residue treated with 80 mL of water. The mixture was extracted with 2 × 250 mL of ether and the ether solution washed with water, 2 × 80 mL of a 10% solution of sodium bisulfite, 2 × 80 mL of a 10% solution of acetic acid, and then again with water. The ether solution was dried (Na_2SO_4) and the solvent removed under reduced pressure to give 46.8 g of a viscous oil. The oil was distilled through a 12 in. Vigreux column (¾ in. diameter) to give 30.3 g (69.3%) of **3**, 95% pure by VPC. An analytical sample recrystallized from ether gave: mp 85–86 °C; IR ($CHCl_3$) 3150 (OH), 1790, 1710 (C=O ester), 1600 cm^{-1} (C=O, C=C); NMR ($CDCl_3$): δ 0.90 (CH_3), 1.27 (6 CH_2), 5.55 (−CH=), 8.95 (OH).

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.13; H, 9.02. Found: C, 67.28; H, 9.25.

3-Hydroxy-5-*n*-pentyl-2-cyclohexene-1-one (4). A solution of 50 g (0.20 mol) of **2** in 200 mL of 20% NaOH was heated on a steam bath for 2.5 h, cooled and extracted with two 100-mL portions of ether. The alkaline aqueous solution was acidified slowly with ca. 80 mL of concentrated hydrochloric acid. The resulting aqueous mixture was stirred and heated on a steam bath for 1 h longer, cooled, and extracted with three 200-mL portions of ether. The ether extracts were washed with water and dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was treated twice with 50 mL of benzene, distilling the solvent each time, to leave 36.5 g (96%) of **4** as a viscous oil which solidified on standing. An anlytical sample prepared from heptane gave: mp 71–73 °C (lit.[20] mp 70–71 °C); IR ($CHCl_3$): 2700–2400 (OH), 1735, 1715 cm^{-1} (C=O); λ_{max}^{MeOH}: 258 (ε 17 000), 280 mμ (ε 13 200); NMR ($CDCl_3$): δ 0.88 (CH_3), 1.33 ($4CH_2$), 5.46 (−CH=).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.53; H, 9.70.

3-Methoxy-5-*n*-pentyl-2-cyclohexen-1-one (5). A solution of 91 g (0.50 mol) of **4** in 300 mL of 5% hydrogen bromide in methanol was stirred at room temperature for 24 h. The volatiles were removed under reduced pressure and the oily residue was dissolved in 700 mL of ether, extracted with four 150-mL portions of a saturated Na_2CO_3 solution, washed with 150 mL of water dried over anhydrous Na_2SO_4, and then distilled at 109 °C (0.06 mm) to give 50 g (51%) of **5**. An analytical sample crystallized from petroleum ether exhibited: mp 43–44 °C; IR ($CHCl_3$): 1650 (C=O), 1610 (enol ether), 1237 cm^{-1} (COC); NMR ($CDCl_3$): δ 0.89 (CH_3), 1.34 ($4CH_2$), 3.68 (OCH_3), 5.37 (−CH=).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.25; H, 10.14.

3,5-Dimethoxy-*n*-amylbenzene (6). A mixture of 3.6 g (0.18 mol) of **5** and 8.9 g (0.04 mol) of cupric bromide in 100 mL of methanol was stirred at room temperature for 24 h and filtered, and the filtrate evaporated under reduced pressure. The residual oil was partitioned between 100 mL of ether and 50 mL of water. The ether layer was separated, washed with two 50-mL portions of saturated Na_2CO_3 solution and 50 mL of water and dried (Na_2SO_4), and the solvent removed under reduced pressure. The dark oil was fractionally distilled to give 3.1 g (82%) of **6**, bp 110 °C (0.05 mm) (lit.[12] bp 199 °C (0.5 mm)); IR ($CHCl_3$): 1610, 1590, 1572 (aromatic), 1230, 1123 cm^{-1} (COC).

Acknowledgments. The authors are grateful to the following members of our Physical Chemistry Department (Director, Dr. R. P. W. Scott): Dr. T. Williams, Mr. S. Traiman, Dr. V. Toome, and Dr. C. G. Scott for the nuclear magnetic resonance, infrared, ultraviolet spectra, and vapor phase chromatographic data, respectively. We also thank Dr. F. Scheidl and his staff for the elemental analysis and we are particularly grateful to Mr. P. Heslin for his capable assistance.

Registry No.—1, 15309-570; **2**, 27871-89-2; **3**, 500-66-3; **4**, 58016-19-8; **5**, 58016-32-3; **6**, 22976-40-5; dimethyl malonate, 108-59-8; 3-hepten-1-one, 1119-44-4; methyl 6-*n*-propyl-2-hydroxy-4-oxocyclohex-2-ene-1-carboxylate, 2787-91-6; 3-undecen-2-one, 10522-37-9; methyl 6-*n*-heptyl-2-hydroxy-4-oxocyclohex-2-ene-1-carboxylate, 27871-93-8; 5-methyl-3-undecen-2-one, 58016-25-4; methyl 6-(1-methylheptyl)-2-hydroxy-4-oxocyclohex-2-ene-1-carboxylate, 27871-96-1; methyl 3-bromo-2-hydroxy-4-oxo-6-*n*-pentylcyclohex-2-ene-1-carboxylate, 27920-61-2; methyl 2,4-dihydroxy-6-*n*-pentylbenzoate, 58016-28-7.

References and Notes

(1) R. S. Cahn, *J. Chem. Soc.*, 1400 (1933).
(2) Y. Ganoi and R. Mechoulam, *J. Am. Chem. Soc.*, **86**, 1646 (1964).
(3) For a leading reference, see "Marijuana: Chemistry, Pharmacology and Patterns of Social Use", A. J. Singer, Ed., *Ann. N.Y. Acad. Sci.*, **191** (1971).
(4) R. E. Fahrenholtz, M. Lurie, and R. W. Kierstead, *J. Am. Chem. Soc.*, **89**, 5934 (1967).
(5) R. G. Razdan and G. R. Handrick, *J. Am. Chem. Soc.*, **92**, 6061 (1970).
(6) R. Mechoulam, *Science*, **168**, 1159 (1970).
(7) L. Crombie and R. Ponsford, *J. Chem. Soc. C.*, 796 (1971).
(8) H. C. Krishnamurty and J. Siva Prasad, *Tetrahedron Lett.*, **29**, 2511 (1975).
(9) A. J. Birch and J. Slabbe, *Tetrahedron Lett.*, **24**, 2079 (1976).
(10) J. R. Cannon, P. R. Cheong, C. J. Fallick, B. H. Hamilton, J. A. McDonald, and G. Vinciquerra, *Aust. J. Chem.*, **26**, 799 (1973).
(11) R. Adams, K. H. Chen, and S. Loewe, *J. Am. Chem. Soc.*, **67**, 1534 (1945).
(12) C. M. Suter and A. W. Weston, *J. Am. Chem. Soc.*, **61**, 232 (1939).
(13) R. Bailey, *Can. J. Chem.*, **52**, 2136 (1974).
(14) R. S. Marmor, *J. Org. Chem.*, **37**, 2901 (1972), and references cited therein.
(15) A. Brossi, A. Focella, and S. Teitel, U.S. Patent 3 919 322 (1975). During the preparation of our manuscript, we became aware of the recent publication by L. Cleaver, J. A. Croft, E. Ritchie, and W. C. Taylor, *Aust. J. Chem.*, **29**, 1989 (1976), which uses a similar approach.
(16) I. G. Tishchenko and L. S. Stanishevskii, *J. Gen. Chem. (USSR)*, **33**, 141–145 (1963); Engl. Translation p 134. We are grateful to our colleague, Dr. H. Gurien, for his kind assistance in the preparation of this compound.
(17) When adduct **2** was treated with bromine at 0 °C the brominated intermediate methyl 3-bromo-2-hydroxy-4-oxo-6-*n*-pentylcyclohex-2-ene-1-carboxylate (mp 103–104 °C) was isolated. Heating of the latter gave the aromatized derivative methyl 2,4-dihydroxy-6-*n*-pentylbenzoate (mp 78–80 °C) which was refluxed with mineral acid to yield olivetol (**3**)
(18) A. W. Fort, *J. Org. Chem.*, **26**, 765 (1961).
(19) A. A. Liebman, D. H. Malarek, A. M. Dorsky, and H. H. Kaegi, *J. Labelled Compd.*, **7**, 241 (1971).
(20) R. Adams, B. R. Baker, and R. B. Wearn, *J. Am. Chem. Soc.*, **62**, 2204 (1940).
(21) Y. Asahina, *Ber.*, **69**, 1644 (1936).
(22) We are grateful to our colleagues, Dr. D. Andrews and Mr. R. Propper, for their contribution in refining this step.