A Cannabinoid Derived Prototypical Analgesic[1]

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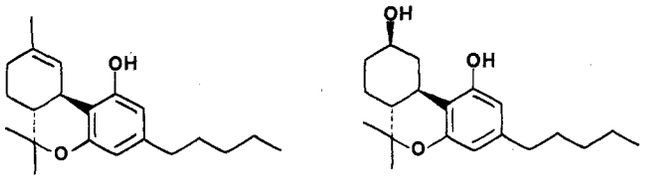
The synthesis and analgesic testing of 3-[4-(1,1-dimethylheptyl)-2-hydroxyphenyl]cyclohexanol (1) are described. Prior (SAR) studies led us to conclude that the pyran ring of 9-nor-9β-hydroxyhexahydrocannabinol (HHC) was not necessary for the expression of biological activity in this series of cannabinoids. Analysis of models and the use of molecular mechanics calculations suggested that a simpler compound, such as 1, would possess the biological activity of HHC. Compound 1 was prepared in nine steps from [3-(benzyloxy)phenyl]acetonitrile (2). Biological testing in five models of pain shows that compound 1 and morphine are equally potent as analgesics and demonstrates that the pyran ring of HHC is not necessary for biological activity. Further simplification of 1 was pursued by the synthesis of 4-[4-(1,1-dimethylheptyl)-2-hydroxyphenyl]-2-pentanol (17), but this derivative exhibits significantly reduced analgesic activity.

The cannabinoid family of natural products is one potential source of new analgesics that, until recently, has been largely ignored.[2,3] The ubiquitous folk medicine from *Cannabis*, marihuana, has endured as a reputed therapy for no fewer than 14 ailments, including the relief of pain. Analgesic activity, among others, has been reported for Δ^9-tetrahydrocannabinol (Δ^9-THC), the major psychoactive



Δ^9-THC HHC

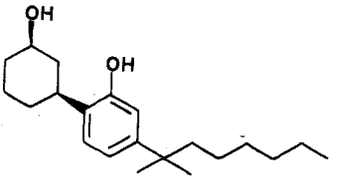
component of marihuana, but results in both animals and humans are equivocal at best.[4,5] A major advance in efforts to dissect meaningful therapeutic activity from Δ^9-THC occurred in the mid 1970's with the disclosure of the enhanced analgesic properties of 9-nor-9β-hydroxyhexahydrocannabinol (HHC) relative to other cannabinoid-like properties.[6] Thus, HHC was the first cannabinoid shown to possess analgesic potency approaching that of morphine in the standard mouse hot plate and mouse tail-flick models of pain. HHC also represented a significant step forward in the search for a nonnarcotic, potent analgesic structurally unrelated to morphine.

While HHC represents an important modification of Δ^9-THC, it still possesses the tricyclic benzopyran skeleton of the prototype. We therefore sought to delineate the minimum structural requirements of HHC needed to produce analgesia. Our selection of a target compound for synthesis was guided by the work of Adams, who first showed that replacement of the C_5H_{11} side chain of cannabinols by higher and branched homologues caused significantly enhanced biological potency,[7] and our own earlier research with such side chains.[8] Thus, we incorporated the 3-(1,1-dimethylheptyl)phenol portion into our target prototype to maximize the effect of the side chain on the structure.

Previously reported work and studies in our laboratories suggested that the dimethyldihydropyran ring portion of HHC was not required for potent biological activity.[8] Unexpectedly, substitution of carbon (phenanthrenes) or nitrogen (phenanthridines) for the oxygen of the pyran ring in HHC yielded compounds that were of similar analgesic potency to HHC. Additionally, we have shown in the work leading to levonantradol that the geminal dimethyl group on the pyran ring of HHC is not necessary for analgesic activity.

Thus, the dihydropyran moiety appeared to serve no other purpose than to firmly anchor the phenolic ring and cyclohexyl ring in an active conformation. This hypothesis led us to further postulate that HHC interacts at a receptor site by a three-point contact,[9] the three binding sites being the equatorial alcohol, phenol, and C-3 side chain.

Taken together, these observations pointed to compound 1 as a target molecule having the minimum structural



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features required for analgesia. The remaining consideration in choosing to synthesize 1 was whether analgesic activity would be dependent on maintenance of a favorable conformational orientation, as in HHC, between the phenol

(1) This paper has been presented in part, see: (a) Melvin, L. S.; Johnson, M. R.; Harbert, C. A.; Milne, G. M. In "Abstracts of Papers", 183rd National Meeting of the American Chemical Society, Las Vegas, NV, Mar 1982, American Chemical Society: Washington, DC, 1982; Abstr MEDI 45. (b) Johnson, M. R.; Melvin, L. S.; Milne, G. M. The International Narcotics Research Conference, North Falmouth, MA, June, 1982; *Life Sci.* **1982**, *31*, 1703. (c) Milne, G. M.; Johnson, M. R.; Koe, B. K.; Weissman, A.; Melvin, L. S. 18th International Meeting of Therapeutic Chemistry, Rennes, France, July 1982.

(2) (a) Mechoulam, R., Ed. "Marihuana"; Academic Press: New York, 1973. (b) Mechoulam, R.; McCallum, N. K.; Burstein, S. *Chem. Rev.* **1976**, *76*, 76. (c) Pars, H. G.; Razdan, R. K.; Howes, J. G. *Adv. Drug Res.* **1977**, *11*, 97. (d) Montgomery, B. J. *JAMA, J. Am. Med. Assoc.* **1978**, *240*, 1469. (e) Bhargava, H. N. *Gen. Pharmacol.* **1978**, *9*, 195. (f) Harris, L. S. In "Mechanism of Pain and Analgesic Compounds"; Beers, R. E., Jr.; Bassett, E. G., Eds.; Raven Press: New York, 1979; p 467. (g) Turner, C. E.; Elsohly, M. A.; Boeren, E. G. *J. Nat. Prod.* **1980**, *43*, 170.

(3) Johnson, M. R.; Milne, G. M. In "Burger's Medicinal Chemistry"; Wolff, M. E. Ed.; Wiley: New York, **1981**, p 699.

(4) Lemberger, L. S. *Annu. Rev. Pharmacol. Toxicol.* **1980**, *20*, 151.

(5) Buxbaum, D. M. *Psychopharmacologia* **1972**, *25*, 275.

(6) Wilson, R. S.; May, E. L.; Martin, B. R.; Dewey, W. K. *J. Med. Chem.* **1976**, *19*, 1165.

(7) Adams, R.; Harfenst, M.; Lowe, S. *J. Am. Chem. Soc.* **1924**, *71*, 1624.

(8) (a) Johnson, M. R.; Althuis, T. H.; Bindra, J. S.; Harbert, C. A.; Melvin, L. S.; Milne, G. M. *NIDA Res. Monogr. Ser.* **1981**, *no. 34*, p 68. (b) Johnson, M. R.; Melvin, L. S.; Althuis, T. H.; Bindra, J. S.; Harbert, C. A.; Milne, G. M.; Weissman, A. *J. Clin. Pharmacol.* **1981**, *21*, 2715.

(9) Milne, G. M.; Johnson, M. R. *J. Clin. Pharmacol.* **1981**, *21*, 367.

0022-2623/84/1827-0067$01.50/0

Table I. Analgesic Activity Test Results

compd	MPE_{50},[a] mg/kg PBQ[b]	RTC[c]	HP[d]	TF[e]	FJ[f]
1	1.0 (0.35-1.62)[g]	4.7 (1.25-7.24)	8.1 (6.9-9.6)	4.4 (3.45-5.52)	4.9 (2.26-7.10)
12	3.8 (1.81-6.17)	12.3 (4.55-64.0)	>56[h]	55.7 (36.0-114)	~17.8[i]
13	4.5 (1.90-7.47)	26.1 (17.9-55.0)	>32[h]	15.3 (12.6-19.6)	11.5 (7.9-16.7)
HHC	0.63[j] (0.26-0.97)	7.0 (4.0-16.8)	34.4 (15.6-174)	9.1 (5.08-21.0)	36.4 (33.3-40.0)
Δ^9-THC	5.9 (1.32-11.3)	29.1 (24.3-36.1)	>178[h]	55[j,k] (32-218)	83.1 (47.8-1217)
morphine	1.8 (1.19-4.74)	4.8 (3.53-5.75)	4.2 (1.98-7.07)	5.7 (2.73-10.6)	10.3 (6.63-13.8)

[a] The dose to produce 50% of the maximum possible effect (subcutaneous). [b] Mouse phenylbenzoquinone-induced writhing, 1 h postdose. [c] Rat tail clamp, 2 h postdose. [d] Mouse hot plate, 1 h postdose. [e] Mouse tail flick, 1 h postdose. [f] Rat flinch jump, 2 h postdose. [g] 95% confidence interval. [h] Less than 50% response at this dose. [i] 59% response at this dose. [j] 20 min postdose. [k] >178 at 1 h postdose.

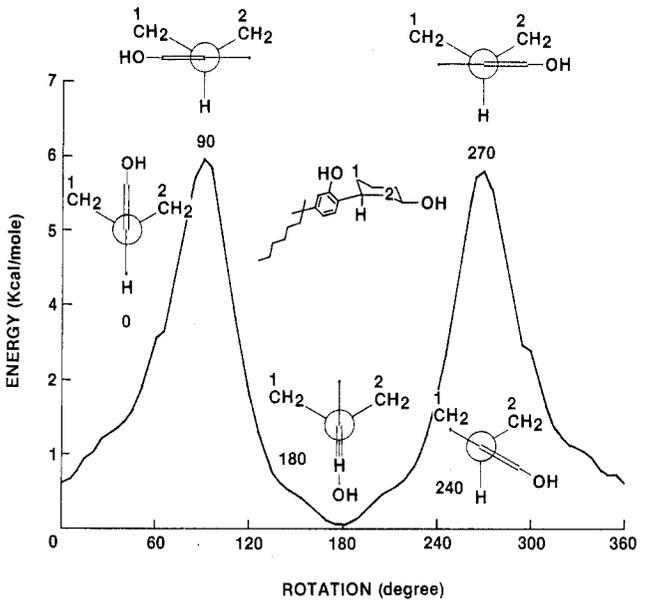


Figure 1. Allinger's MMI calculation for 1 in 5° increments of rotation about the aryl–cyclohexyl ring bond. The 240° Newman projection overlaps the calculated least-energy conformation of HHC.

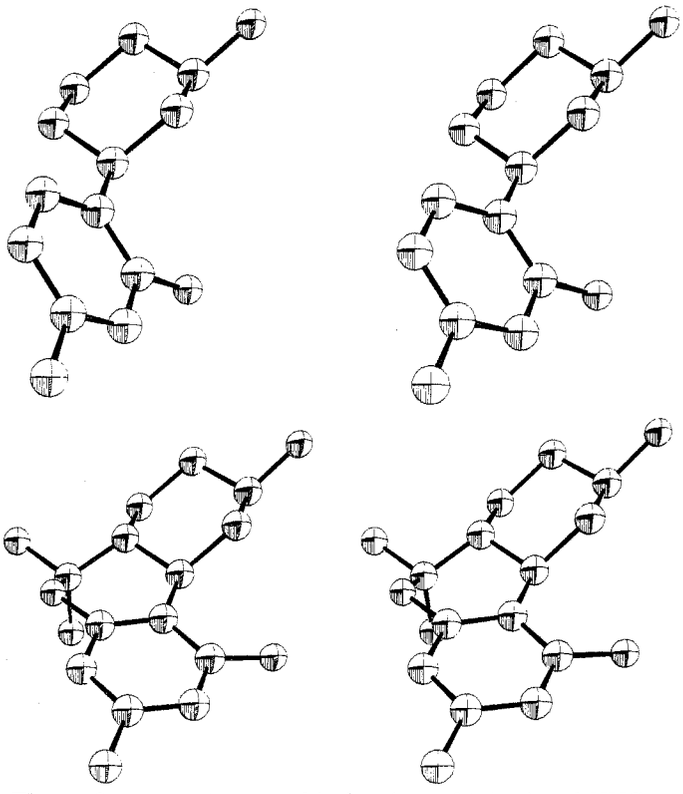


Figure 2. ORTEP stereographic drawings of 1 (top) and HHC (bottom) in minimum-energy conformations calculated from Allinger's MMI program. The 1,1-dimethylheptyl and *n*-pentyl side chains were abbreviated for simplicity.

and alcohol functionalities. Examination of Dreiding models of 1 relative to the conformationally rigid HHC molecule, however, revealed that structure 1 could readily adopt the orientation of the phenol and alcohol existing in HHC. Furthermore, a more detailed probe of energy vs. conformation, using Allinger's molecular mechanics calculation program, MMI,[10] predicted a conformational energy minimum for 1, wherein the three proposed points of receptor bindng (alcohol, phenol, and aryl side chain) are nearly coincidental with those similarly calculated for HHC. These points are illustrated by the MMI[10] generated curve in Figure 1, which represents the conformational energy of 1 as a function of rotation about the bond connecting the aromatic and cyclohexyl rings. Figure 2 shows a set of stereo models for the calculated minimum-energy conformation of 1 and HHC in which the gross conformational similarities are clearly discernible.

We report herein the synthesis of 1 and the biological evaluation of this prototype and several analogues as analgesics.

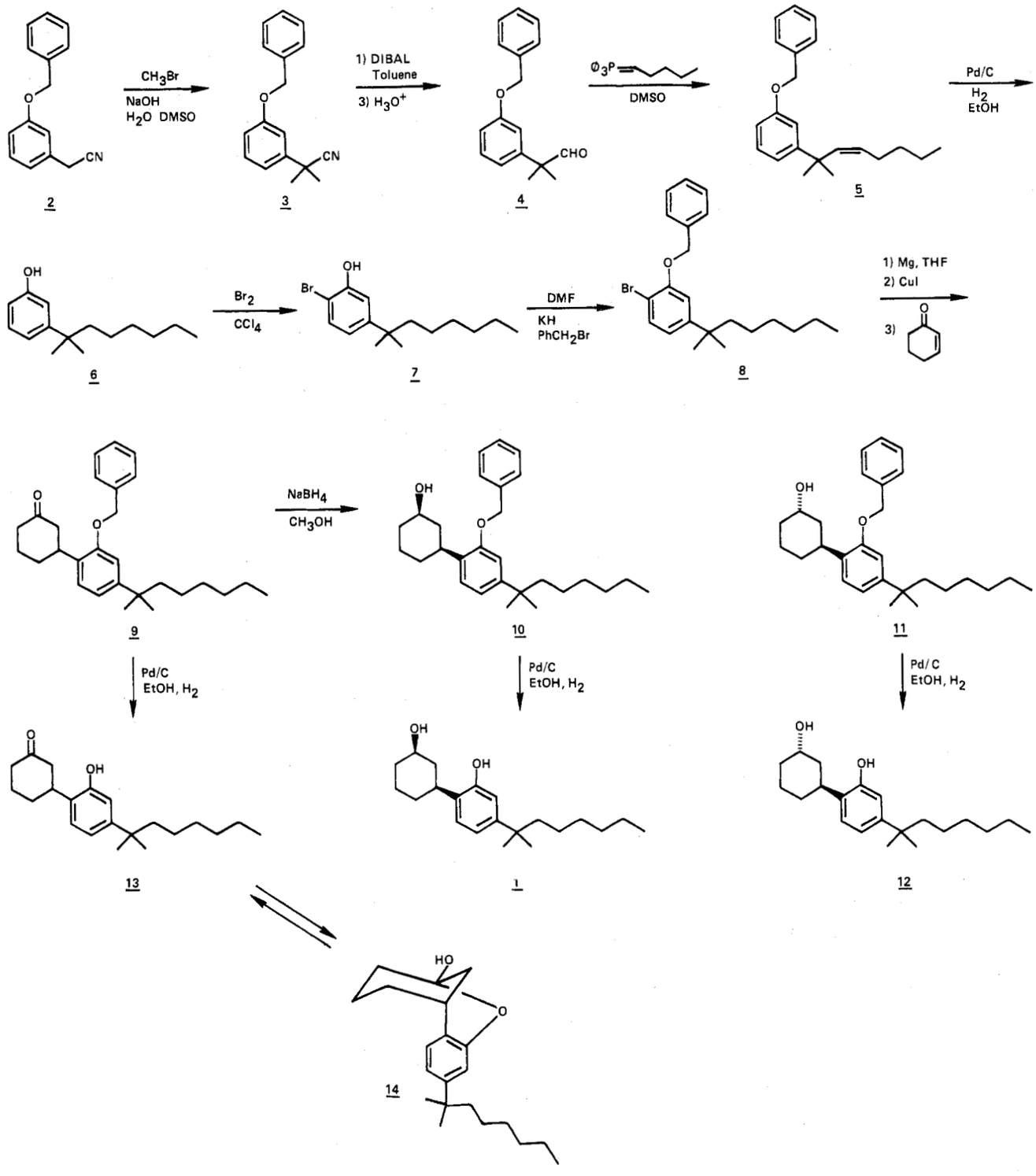
Chemistry. The phenolic side-chain portion of prototype 1 is prepared (Scheme I) from the nitrile **2**,[11] which is first alkylated (98% yield), reduced with diisobutylaluminum hydride, and then hydrolyzed to aldehyde **4** (99%). The crude aldehyde **4** is reacted via the Wittig condensation to yield olefin **5** (57%). Catalytic hydrogenation of **5** provides 3-(1,1-dimethylheptyl)phenol, **6** (78%). Bromination of **6** occurs regioselectively and is followed by benzylation to afford the desired Grignard precursor **8** (100%).

Cuprous ion catalyzed conjugate addition of the Grignard reagent generated from **8** with cyclohexenone gives ketone **9** in 79% yield. Sodium borohydride reduction of ketone **9** in methanol gives a 4:1 ratio of epimeric alcohols **10** and **11** (63%). Low reduction temperatures favor the formation of cis-alcohol **10**, while reduction of ketone **9** with K-Selectride yields predominately the trans-alcohol **11**. The required cis-alcohol **10** is hydrogenolyzed over palladium on carbon to yield racemic 1 (77%), and the trans-alcohol **11** similarly yields **12** (71%).

Hydrogenolysis of **9** provides the phenolic ketone **13** (62%), which is shown by lack of a carbonyl absorption in the infrared and NMR analysis to exist in the hemiketal form **14**. Sodium borohydride reduction of **14** yields a mixture of alcohols **1** and **12**; however, this mixture is less easily separated than that of **10** and **11**.

(10) Allinger, N. L. *QCPE* **1976**, 381.
(11) Pinder, R. M.; Burger, A.; Ariëns, E. J. *Arzneim.-Forsch.* **1970**, *20*, *245*.

Scheme I



Results and Discussion

Prototype 1 and three standards were screened in a battery of assays (see Table I) to measure relief of pain induced by chemical, pressure, thermal, and electrical stimuli. The data illustrated similar broad analgesic profiles for prototype 1, HCC, and morphine. Testing of 1 in animal behavioral models (mouse rotorod, rat sedation, and dog ataxia) suggests that it possesses cannabinoid-like effects in common with HHC and Δ^9-THC.[12] These results are especially noteworthy, since prototype 1 lacks both the benzopyran ring and rigidity of HHC and most conspicuously lacks the basic nitrogen of morphine.[13]

The effect of oxidation state and stereochemistry on the analgesic activity of 1 is also shown in Table I. The equatorial alcohol 1 is several fold more potent than the ketone 13 or axial alcohol 12. This is of interest, since in vivo metabolic interconversion of the three compounds is possible. If such interconversion is occurring, these data would suggest that it is slow relative to onset of biological activity.

(12) Results of testing 1 in animal behavioral models have been reported elsewhere: Weissman, A.; Milne, G. M.; Melvin, L. S. *J. Pharmacol. Exp. Ther.* **1982**, *223*, 516.

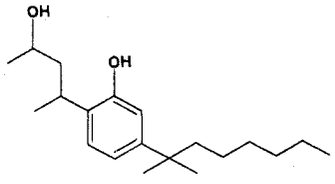
(13) Andrews, P. R.; Lloyd, E. J. *Med. Chem. Rev.* **1982**, *2*, 355.

Table II. Mouse Phenylbenzoquinone Writhing (PBQ)

compd	PBQ, % inhibn (dose,[a] mg/kg sc)
17a	55 (56)
17b	27 (10), 52 (32), 50 (56), 53 (100)
18	0 (56)

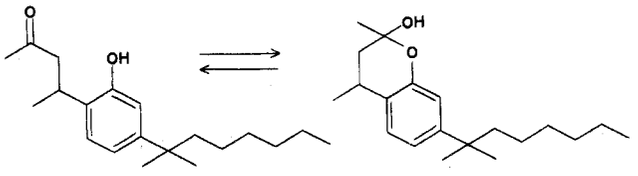
[a] 1 h postdose.

To determine the smallest analgesically active fragment of HHC, we found it necessary to remove another ring from 1. This was accomplished by the synthesis (see Experimental Section) of the pentanol diastereomers **17** in which



17a,b

the cyclohexyl ring of 1 is opened. While **17** does possess analgesic activity as measured by the PBQ test (see Table II), the potency is dramatically reduced and the activity is not dose responsive. The pentanone **18**, in equilibrium



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with a hemiketal, is seen to be inactive in the PBQ test. Thus, the rigidity of the cyclohexyl ring seems to be required for the potent analgesic activity of 1.

Based on these results, we believe that 1 is an important, structurally novel analgesic prototype that conclusively demonstrates the nonessential nature of the pyran ring of HHC for the expression of biological activity.

Experimental Section

Melting points were determined with open capillary tubes in a Thomas-Hoover apparatus and are uncorrected. ^{1}H NMR spectra, obtained on a Varian T-60 or XL-100 spectrometer, were recorded in $CDCl_3$, unless otherwise noted, and data are reported as δ values with respect to Me_4Si. IR spectra, obtained on a Perkin-Elmer 237B spectrophotometer, were recorded in $CHCl_3$, unless otherwise noted, and data are reported in reciprocal centimeters. High-resolution mass spectra were obtained on an AEI-MS30 coupled with a DS-50 system. Column chromatography was carried out on EM Reagents silica gel 60. When analyses are indicated only by symbols of the elements, the analytical results obtained are within 0.4% of the theoretical values. Biological assays have been described previously[14] for mouse writhing,[15] mouse hot plate,[16] mouse tail flick,[17] rat flinch jump,[18] and rat tail clamp.[19]

2-[3-(Benzyloxy)phenyl]-2-methylpropionitrile (3). To a solution of 1.5 L of Me_2SO saturated with CH_3Br were simultaneously added a solution of **2**[11] (295 g, 1.32 mol) in 200 mL of Me_2SO and a solution of 50% aqueous NaOH (420 mL). CH_3Br was continuously bubbled through the reaction mixture during the above addition (30 min) and then for 1.5 h longer while the reaction temperature was maintained at ≤50 °C with ice cooling. The reaction mixture was added to 2 L of H_2O–2 kg of ice, and the resultant mixture extracted with four 1-L portions of Et_2O. The combined organic extract was washed twice with 1 L of H_2O and once with 1 L of saturated NaCl, dried ($MgSO_4$), and evaporated to give 325 g (98%) of **3** as an oil: NMR δ 1.70 (6 H, s, CH_3), 5.12 (2 H, s, CH_2), 6.8–7.5 (4 H, m, aromatic), 7.45 (5 H, s, aromatic); IR 2247 (C≡C) cm^{-1}; MS, *m/e* 251 (M^+).

2-[3-(Benzyloxy)phenyl]-2-methylpropionaldehyde (4). To a 15 °C solution of **3** (325 g, 1.25 mol) in 1.85 L of THF was added 1.6 mol of diisobutylaluminum hydride as a 1.3 M solution in hexane (reaction temperature is maintained at 15–18 °C). The reaction mixture was allowed to warm to 25 °C and then stirred for an additional 2 h. The reaction was hydrolyzed by the addition to a cold solution of 170 mL of H_2SO_4 in 670 mL of H_2O (temperature maintained <30 °C). The resultant mixture was allowed to warm to 25 °C and then stirred 2 h longer. The organic layer was separated, and the aqueous phase was extracted once with 1 L of Et_2O. The combined organic extract was washed with 0.5 L of H_2O and 0.5 L of saturated NaCl, dried ($MgSO_4$), and evaporated to yield 315 g (99%) of **4** as an oil: NMR δ 1.43 (6 H, s, CH_3), 5.0, (2 H, s, CH_2), 6.8–7.5 (4 H, m, aromatic), 8.4 (5 H, s, aromatic), 9.55 (1 H, s, CHO); IR 1742 (C=O), 1613 (C=C) cm^{-1}; MS, *m/e* 254 (M^+).

1-(Benzyloxy)-3-(1,1-dimethyl-2-heptenyl)benzene (5). To a 15 °C solution of 1.8 mol of dimsyl sodium (from NaH and Me_2SO) in 2 L of Me_2SO was added, portionwise, pentyltriphenylphosphonium bromide (768 g, 1.8 mol). The resultant slurry was stirred for 15 min at 15–20 °C, and then **4** (315 g, 1.24 mol) was slowly added (reaction temperature maintained at <30 °C). The resultant mixture was stirred for 4 h at 15 °C and then added to 6 L of ice. The quenched reaction was extracted with four 1-L portions of 50% Et_2O–pentane. The combined extract was washed twice with 1 L of H_2O and once with 1 L of saturated NaCl, dried ($MgSO_4$), and evaporated to an oil. Crystallization and evaporation of the filtrate gave 559 g of oil. This crude oil was purified via column chromatography on 2 kg of silica gel eluted with 20% hexane–CH_2Cl_2 to yield 217 g (57%) of **5** as an oil: NMR δ 0.75 (3 H, br t, J = 6 Hz, CH_3), 1.1 (4 H, m, CH_2), 1.43 (6 H, s, CH_3), 1.60 (2 H, m, CH_2C=), 5.09 (2 H, s, CH_2), 5.28 (1 H, dt, J = 12 and 6 Hz, vinyl H), 5.70 (1 H, dd, J = 12 and 1 Hz, vinyl H), 6.7–7.5 (4 H, m, aromatic), 7.42 (5 H, s, aromatic); IR 1610 and 1587 (C=C) cm^{-1}; MS, *m/e* 308 (M^+).

3-(1,1-Dimethylheptyl)phenol (6). A mixture of **5** (65 g, 0.211 mol) and 7.5 g of 10% Pd/C in 100 mL of EtOH was hydrogenated for 1 h on a Parr apparatus at 50 psi of H_2 pressure. Additional 7.5-g portions of 10% Pd/C were added after 1 and 2 h of reaction, and the reaction continued for 12 h longer. The reaction mixture was filtered through diatomaceous earth with EtOH, and the filtrate was exaporated to an oil. The oil was purified via column chromatography on 1 kg of silica gel eluted with 50% hexane–CH_2Cl_2 to yield 105 g (78%) of **6** as an oil: NMR δ 0.85 (3 H, br t, CH_3), 1–1.9 (10 H, m, CH_2), 1.29 (6 H, s, CH_3), 4.98 (1 H, s, OH), 6.6–7.4 (4 H, m, aromatic); IR 3571, 3311 (OH), 1592 (C=C) cm^{-1}; MS, *m/e* 220 (M^+).

2-Bromo-5-(1,1-dimethylheptyl)phenol (7). To a 0 °C solution of **6** (110 g, 0.5 mol) in 200 mL of CCl_4 was added dropwise a solution of Br_2 (80 g, 0.5 mol) in 90 mL of CCl_4 (reaction temperature maintained at ≤30 °C with ice cooling). The reaction mixture was stirred for an additional 15 min and then evaporated to yield 150 g (100%) of **7** as an oil: NMR δ 0.85 (3 H, br t, CH_3), 0.8–1.9 (10 H, m, CH_2), 1.28 (6 H, s, CH_3), 5.4 (1 H, br s, OH), 6.78 (1 H, dd, J = 8 and 2 Hz, C-6 aromatic H), 7.02 (1 H, d, J = 2 Hz, C-2 aromatic H), 7.37 (1 H, d, J = 8 Hz, C-5 aromatic H); IR 3559, 3289 (OH), 1585 (C=C) cm^{-1}; MS, *m/e* 300, 298 (M^+).

2-(Benzyloxy)-1-bromo-4-(1,1-dimethylheptyl)benzene (8). To a −18 °C slurry of KH (23.0 g, 0.575 mol) in 400 mL of DMF was added over a 45-min period a solution of **7** (150 g, 0.5 mol) in 400 mL of DMF. The reaction mixture was stirred 15 min longer, after which a solution of benzyl bromide (98.3 g, 0.575 mol) in 200 mL of DMF was added. The reaction mixture was then allowed to warm to 25 °C and stirred for 30 min longer. The reaction was quenched by the addition to 6 L of ice. The quenched

(14) McIlhenny, H. M.; Mast, R. W.; Johnson, M. R.; Milne, G. M. *J. Pharmacol. Exp. Ther.* **1981**, *219*, 363.
(15) Milne, G. M.; Koe, B. K.; Johnson, M. R. *NIDA Res. Monogr. Ser.* **1980**, *no. 27*, p 84.
(16) Woolfe, G.; MacDonald, A. D. *J. Pharmacol. Exp. Ther.* **1944**, *80*, 300.
(17) D'Amour, F. E.; Smith, D. L. *J. Pharmacol. Exp. Ther.* **1941**, *72*, 74.
(18) (a) Evans, W. D. *Psychopharmacologia* **1961**, *2*, 318. (b) Tenen, S. S. *Ibid.* **1968**, *12*, 278.
(19) Haffner, F. *Deutsch. Med. Wochenschr.* **1929**, *55*, 731.

mixture was extracted six times with 0.5 L of Et_2O. The combined extract was washed twice with 1-L portions of H_2O and once with 1 L of saturated NaCl, dried ($MgSO_4$), and evaporated to give a quantitative yield of **8**: NMR δ 0.85 (3 H, br t, CH_3), 0.8–2.0 (10 H, m, CH_2), 1.22 (6 H, s, CH_3), 5.17 (2 H, s, CH_2), 6.7–7.6 (8 H, m, aromatic H); IR 1592 and 1575 (C=C) cm^{-1}; MS, *m/e* 390.1407 (calcd for $C_{22}H_{29}BrO$, 390.1375).

3-[2-(Benzyloxy)-4-(1,1-dimethylheptyl)phenyl]cyclohexanone (9). A solution of **8** (75.0 g, 0.193 mol) in 200 mL of THF was slowly added to 70–80 mesh Mg (9.25 g, 0.386 mol). The resultant mixture was refluxed for 20 min and then cooled to −18 °C. CuI (1.84 g, 9.7 mmol) was added, and stirring was continued for 10 min. To the resultant mixture was slowly added a solution of 2-cyclohexen-1-one (18.5 g, 0.193 mol) in 40 mL of THF at such a rate that the reaction temperature was maintained <−3 °C with NaCl–ice cooling. The reaction was stirred 30 min longer and then added to 500 mL of 2 N HCl and 2 L of ice–water. The quenched reaction was extracted three times with 500-mL portions of ether. The combined extract was washed twice with 100 mL of water and twice with 100 mL of saturated NaCl, dried ($MgSO_4$), and evaporated to an oil. The oil was purified via column chromatography on 1.6 kg of silica gel eluted with 20% Et_2O–cyclohexane to yield 62.5 g (79%) of **9** as an oil: NMR δ 0.84 (3 H, m, CH_3), 1.27 (6 H, s, CH_3), 3.32 (1 H, m, benzylic CH), 5.06 (2 H, s, CH_2), 6.7–7.3 (3 H, m, aromatic H), 7.32 (5 H, s, aromatic H); IR 1709 (C=O), 1613, 1575 (C=C) cm^{-1}; MS, *m/e* 406 (M^+).

(*E*)- and (*Z*)-3-[2-(Benzyloxy)-4-(1,1-dimethylheptyl)-phenyl]cyclohexanol (10 and 11). To a −40 °C solution of **9** (4.30 g, 0.106 mol) in 500 mL of MeOH and 15 mL of THF was added $NaBH_4$ (8.05 g, 0.212 mol). The reaction mixture was stirred for 1 h at −40 °C, allowed to warm to −10 °C, and then quenched by the addition of 100 mL of saturated NaCl. The quenched reaction was diluted with 1.5 L of H_2O and extracted with three 450-mL portions of Et_2O. The combined extract was washed three times with 100 mL of H_2O and twice with 200 mL of saturated NaCl, dried ($MgSO_4$), and evaporated to an oil. The oil was purified via column chromatography on 400 g of silica gel eluted with 20% Et_2O–cyclohexane to yield, in order of elution, 5.0 g of **11** (12%) as an oil: NMR δ 0.85 (3 H, m, CH_3), 1.26 (6 H, s, CH_3), 3.51 (1 H, m, benzylic CH), 4.24 (1 H, m, CH), 5.15 (2 H, s, CH_2), 6.85–7.26 (3 H, m, aromatic H), 7.47 (5 H, m, aromatic H); IR 3636, 3497 (OH), 1629, 1587 (C=C) cm^{-1}; MS, *m/e* 408 (M^+). Anal. ($C_{28}H_{40}O_2$) C, H. Yield of **10**: 22.2 g (51%) as a solid from hexane: mp 75.5–76.5 °C; NMR δ 0.85 (3 H, m, CH_3), 1.28 (6 H, s, CH_3), 3.1 (1 H, m, benzylic CH), 3.79 (1 H, m, CH), 5.12 (2 H, s, CH_2), 6.83–7.22 (3 H, m, aromatic H), 7.42 (5 H, s, aromatic H); IR 3636, 3497 (OH), 1629, 1587 (C=C) cm^{-1}; MS, *m/e* 408 (M^+). Anal. ($C_{28}H_{40}O_2$) C, H.

(*Z*)-3-[4-(1,1-Dimethylheptyl)-2-hydroxyphenyl]cyclohexanol (1). A mixture of **10** (2.20 g, 5.39 mmol), $NaHCO_3$ (12 g), and 10% Pd/C (2.0 g) in 100 mL of EtOH was stirred under 1 atm of H_2 for 2 h. The reaction mixture was filtered through diatomaceous earth, and the filtrate was evaporated to a solid. The solid was recrystallized from hexane to yield 1.32 g (77%) of **1**: mp 109–110 °C; NMR δ 0.81 (3 H, m, CH_3), 1.25 (6 H, s, CH_3), 2.80 (1 H, m, benzylic H), 3.80 (1 H, m, CH), 5.4 (1 H, br, OH), 6.63 (1 H, br s, aromatic H), 6.77 (1 H, dd, J = 8 and 2 Hz, aromatic H), 6.87 (1 H, d, J = 8 Hz, aromatic H); IR 3610, 3356 (OH), 1626, 1582 (C=C) cm^{-1}; MS, *m/e* 318 (M^+). Anal. ($C_{21}H_{34}O_2$) C, H.

(*E*)-3-[4-(1,1-Dimethylheptyl)-2-hydroxyphenyl]cyclohexanol (12). By the procedure used for **1**, compound **11** (4.50 g, 11 mmol) gave 2.47 g (71%) of **12** recrystallized from pentane: mp 124–125 °C; NMR δ 0.81 (3 H, m, CH_3), 1.25 (6 H, s, CH_3), 3.25 (1 H, m, benzylic H), 4.22 (1 H, m, CH), 6.81 (1 H, d, J = 2 Hz, aromatic H), 6.81 (1 H, dd, J = 8 and 2 Hz, aromatic H), 7.08 (d, J = 8 Hz, aromatic H); IR 3610, 3390 (OH), 1626, 1575 cm^{-1}; MS, *m/e* 318 (M^+). Anal. ($C_{21}H_{34}O_2$) C, H.

3-[4-(1,1-Dimethylheptyl)-2-hydroxyphenyl]cyclohexanone (13). By the procedure used for **1**, compound **9** (19.5 g, 46.8 mmol) gave 9.1 g (62%) of **13** recrystallized from aqueous methanol: mp 87 °C; NMR δ 0.87 (3 H, m, CH_3), 1.27 (6 H, s, CH_3), 1.0–2.2 (several m), 3.21 (2 H, m), 6.92 (3 H, m, aromatic H); IR (KBr) 3226 (OH), 1629, 1580 (C=C) cm^{-1}; IR ($CHCl_3$) 3571, 3289 (OH), 1704 (w, C=O), 1623, 1575 cm^{-1}; MS, *m/e* 316 (M^+). Anal. ($C_{21}H_{32}O_2$) C, H.

4-[2-(Benzyloxy)-4-(1,1-dimethylheptyl)phenyl]-2-pentanone (15). By the procedure used for **9**, 3-penten-2-one (1.26 g, 15.4 mmol) and **8** (6.00 g, 15.4 mmol) yield 3.99 g (66%) of **15** as an oil: NMR δ 0.81 (3 H, m, CH_3), 1.24 (6 H, s, CH_3), 2.00 (3 H, s, CH_3CO), 2.65 (2 H, m, CH_2), 3.2–4.0 (1 H, m, CH), 5.07 (2 H, s, CH_2), 6.85 (2 H, m, aromatic H), 7.07 (1 H, d, J = 8 Hz, aromatic H), 7.34 (5 H, br s, aromatic H); IR 1715 (C=O), 1613, 1575 (C=C) cm^{-1}; MS, *m/e* 394 (M^+).

4-[2-(Benzyloxy)-4-(1,1-dimethylheptyl)phenyl]-2-pentanol (16a,b). By the procedure used for **10**, compound **15** (1.8 g, 4.60 mmol) gave 273 mg (15%) of diastereomer **16a** as an oil [NMR δ 0.85 (3 H, m, CH_3), 1.08 (3 H, d, J = 6 Hz, CH_3), 1.29 (6 H, s, CH_3), 3.5 (2 H, m, CH), 5.09 (2 H, s, CH_2), 7.0 (3 H, m, aromatic H), 7.40 (5 H, br s, aromatic H); IR 3497 (OH), 1613, 1572 (C=C) cm^{-1}; MS, *m/e* 396 (M^+)] and 825 mg (45%) of diastereomer **16b** as an oil [NMR δ 0.85 (3 H, m, CH_3), 1.28 (6 H, s, CH_3), 3.40 (1 H, m, CH), 3.80 (1 H, m, CH), 5.10 (2 H, s, CH_2), 6.90 (2 H, m, aromatic H), 7.17 (1 H, d, J = 8 Hz, aromatic H), 7.42 (5 H, br s, aromatic); IR 3546 (OH), 1616, 1575 (C=C) cm^{-1}; MS, *m/e* 396 (M^+)].

4-[4-(1,1-Dimethylheptyl)-2-hydroxyphenyl]-2-pentanol (17a,b). By the procedure used for **1**, compound **16a** (236 mg, 0.595 mmol) gave 179 mg (98%) of **17a** as an oil: NMR δ 0.85 (3 H, m, CH_3), 1.28 (6 H, s, CH_3), 3.50 (2 H, m, CH), 6.82 (1 H, d, J = 2 Hz, aromatic H), 6.84 (1 H, dd, J = 8 and 2 Hz, aromatic H), 7.16 (1 H, d, J = 8 Hz, aromatic H); IR 3610, 3333 (OH), 1634, 1577 (C=C) cm^{-1}; MS, *m/e* 306.2577 (calcd for $C_{20}H_{34}O_2$, 306.2559). Compound **16b** (804 mg, 2.03 mmol) gave 621 mg (100%) of **17b** as an oil: NMR δ 0.85 (3 H, m, CH_3), 3.19 (1 H, sextet, J = 6 Hz, CH), 3.99 (1 H, sextet, J = 6 Hz, CH), 6.82 (1 H, d, J = 2 Hz, aromatic H), 6.88 (1 H, dd, J = 8 and 2 Hz, aromatic H), 7.13 (1 H, d, J = 8 Hz, aromatic H); IR 3610, 3378 (OH), 1629, 1575 cm^{-1}; MS, *m/e* 306 (M^+). Anal. ($C_{20}H_{34}O_2$) C, H.

4-[4-(1,1-Dimethylheptyl)-2-hydroxyphenyl]-2-pentanone (18). By the procedure used for **1**, compound **15** (1.8 g, 4.60 mmol) gave 490 mg (35%) of **18** recrystallized from pentane: mp 79.5–80.5 °C; NMR δ 0.84 (3 H, m, CH_3), 1.27 (6 H, s, CH_3), 1.64 and 2.07 (3 H, s, hemiketal and ketone CH_3 respectively), 2.5–3.5 (3 H, m, CH, CH_2), 6.75–7.25 (3 H, m, aromatic H); IR (KBr) 3448 (OH), 1626, 1577 cm^{-1}; IR ($CHCl_3$) 3571, 3333 (OH), 1706 (w, C=O), 1623, 1572 cm^{-1}; MS, *m/e* 304 (M^+). Anal. ($C_{20}H_{32}O_2$) C, H.

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