also provides the first total synthesis of the corresponding unnatural (+) enantiomorph.

These syntheses depended initially on the observation that, since the cinnamic acid I,[9] from its method of preparation by the Knoevenagel reaction of malonic acid with the corresponding aldehyde, should have the *anti* configuration, it may be predicted, from the rule governing the retention of configuration of the dienophile constituents in the Diels–Alder reaction (*e.g.*, see ref 10), that the racemic adduct of I with isoprene[9] should have the *trans* configuration II analogous to that found in Δ^8- and Δ^9-tetrahydrocannabinol.[2,6,11] The *anti* configuration of I is confirmed by the pmr spectrum, in which the olefinic protons display a coupling constant, J, of 16.5 cps, in good agreement with the value of 17 cps observed for *anti*-styrenoid protons and quite distinct from the value of 10 cps found for corresponding *syn* protons.[12] The racemic adduct II, from I and isoprene, mp 114–116° (lit.[9] 115–115.5°), was resolved by fractional crystallization of its diastereoisomeric (+)-1-1'-naphthylethylamine salts from hexane. Fusion of the resulting (−)-II,[13] mp 137.5–138.5°, $[\alpha]^{24}$D −63° (*c* 1.00, CHCl₃), with methylmagnesium iodide at 165°[1,14] demethylated the dimethoxybenzene ring and converted the carboxyl to a 2-hydroxylpropyl group giving what, from its infrared and pmr absorption spectra, is probably the crude triol III, and the latter, on distillation (bath temperature 200° (0.01 mm)) and filtration in benzene through neutral Al₂O₃, gave in 47% over-all yield from II a gum, $[\alpha]^{24}$D −173° (*c* 1.20, C₂H₅OH),[15] which was separated by preparative glpc[16] into pure (−)-Δ^8-tetrahydrocannabinol (IV) obtained as a gum $[\alpha]^{24}$D −256° (*c* 0.99, C₂H₅OH) (lit. −266°,[11b] −260°[7]). The 100-Mcps pmr spectrum[17] displayed the following signals: three-proton triplet at δ 0.88, J = 6 cps (ω-CH₃); three-proton singlets at δ 1.09 and 1.36 (*gem*-CH₃); three-proton singlet at δ 1.70 (C₉ CH₃); two-proton triplet at δ 2.43 (benzylic CH₂); one-proton broad doublet at δ 3.18, half-band width 15 cps (C₁₀ₐ H); one-proton broad multiplet at δ 5.42 (C₈ H); one-proton doublets at δ 6.08 and 6.26, J for both = 1.6 cps (C₂ and C₄ H), in excellent agreement with

the values given[2] for (±)-IV except for a 0.07-ppm discrepancy for the C₁₀ₐ proton signal, which may be due to differences in estimating the center of this broad signal in the two spectra. The mass spectrum[18] showed principal ions at *m/e* 314, 299, 271, 258, 246, 243, 231, and 193, in accord with the data presented for an authentic sample.[19]

The residual salts from the foregoing resolution were decomposed with 3 *N* hydrochloric acid and the resulting acid was resolved by fractional crystallization of its (−)-1-1'-naphthylethylamine salts from hexane to give the unnatural enantiomorph (+)-II, mp 137.5–138.5°, $[\alpha]^{24}$D +63° (*c* 1.07, CHCl₃), which was converted, as for (−)-II, to (+)-IV, $[\alpha]^{24}$D +250° (*c* 1.04, C₂H₅OH), which was chromatographically and spectrographically identical with (−)-IV.

Biological testing is currently underway with (±)-IV and will be extended to both of the constituent enantiomorphs. The authors hope to report the results in a later full communication.

(18) Measured on the Atlas CH-4 mass spectrometer.
(19) U. Claussen, H.-W. Fehlhaber, and F. Korte, *Tetrahedron*, **22**, 3535 (1966).

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A Stereospecific Synthesis of (−)-Δ^1- and (−)-$\Delta^{1(6)}$-Tetrahydrocannabinols[1]

Sir:

A number of total syntheses of racemic Δ^1-tetrahydrocannabinol (Δ^1-THC) (I) and $\Delta^{1(6)}$-THC (II) have been published recently.[2] No resolution has been reported so far, and hence these syntheses are of limited value in psychobiological research for which compounds with the natural modification are required.[3]

We report now a facile, stereospecific synthesis leading to (−)-$\Delta^{1(6)}$-THC and thence to (−)-Δ^1-THC. A pinane derivative was chosen as a starting material for the following reasons: (i) its bulky dimethyl-

(9) R. Adams and R. B. Carlin, *J. Am. Chem. Soc.*, **65**, 360 (1943).
(10) J. G. Martin and R. K. Hill, *Chem. Rev.*, **61**, 537 (1961).
(11) (a) R. Mechoulam and Y. Shvo, *Tetrahedron*, **19**, 2073 (1963); (b) Y. Gaoni and R. Mechoulam, *ibid.*, **22**, 1481 (1966).
(12) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 238.
(13) This substance, its enantiomorph, and (+)- and (−)-IV gave satisfactory elemental analyses.
(14) V. Grignard and J. Ritz, *Bull. Soc. Chim. France*, **3**, 1181 (1936); W. Salzer, *Z. Physiol. Chem.*, **274**, 39 (1942); A. L. Wilds and W. B. McCormack, *J. Am. Chem. Soc.*, **70**, 4127 (1948).
(15) Optical rotations were measured on a Carl Zeiss photoelectric precision polarimeter, accurate to 0.005°.
(16) Using N₂ as the carrier gas in a Varian Aerograph Autoprep Model 705 gas chromatograph having a 10-ft column (0.375 in. o.d.) at 280° packed with 45–60 mesh Gas Chrom P containing 20% (w/w) SE-30; 20-mg samples were injected in 0.2 ml of CH₂Cl₂. The crude material had previously been shown to be 70–75% pure by glpc using He at a flow rate of 40 cc/min as the carrier gas in a Perkin-Elmer Model 881 chromatograph having a 6-ft column (0.25 in. o.d.) packed with 80–100 mesh AW DMCS Chrom G maintained isothermally at 150° for 1 min and thereafter programmed at 4°/min to 250°, the sample being injected in CH₂Cl₂ at 250°. Under these conditions IV had a retention time of 24 min, the main impurity had a retention time of 22 min, and trace impurities appeared at retention times of 20, 21, 24.7, and 25 min.
(17) Measured on the Varian HA-100 spectrometer using 2–3% solutions in CDCl₃ containing tetramethylsilane as the internal reference standard. Chemical shifts are given in δ units as parts per million measured downfield from the reference, and coupling constants are given in cycles per second.

(1) Hashish. XI. For part X see R. Mechoulam and Y. Gaoni, *Tetrahedron Letters*, 1109 (1967).
(2) (a) R. Mechoulam and Y. Gaoni, *J. Am. Chem. Soc.*, **87**, 3273 (1965); (b) E. C. Taylor, K. Lenard, and Y. Shvo, *ibid.*, **88**, 367 (1966); (c) K. E. Fahrenholtz, M. Lurie, and R. W. Kierstead, *ibid.*, **88**, 2079 (1966).
(3) The isolation from natural sources of both (−)-Δ^1-THC,[4] the major active constituent of hashish, and (−)-$\Delta^{1(6)}$-THC,[5] a minor active component in some marijuana samples, is rather tedious and not practical. Semisynthetic preparations from the more abundant cannabidiol (III) have, however, been described.[4–6] The structures of I, II, and III as written in this paper correspond to the absolute configuration of the naturally occurring (−) modifications.[1,7]
(4) Y. Gaoni and R. Mechoulam, *J. Am. Chem. Soc.*, **86**, 1646 (1964).
(5) R. L. Hively, W. A. Mosher, and F. W. Hoffmann, *ibid.*, **88**, 1832 (1966).
(6) Y. Gaoni and R. Mechoulam, *Tetrahedron*, **22**, 1481 (1966).
(7) T. Petrzilka, W. Haefliger, C. Sikemeier, G. Ohloff, and A. Eschenmoser, *Helv. Chim. Acta*, **50**, 719 (1967).

methylene bridge was expected to provide stereochemical control of the reactions; (ii) as optically pure α-pinene is readily available in both the (+) and (−) modifications, an entry into the natural (−) and unnatural (+) series was envisaged.

(−)-Verbenol[8] was condensed with olivetol in methylene chloride in the presence of p-toluenesulfonic acid to give a mixture of three oily compounds, which were easily separated by chromatography on Florisil. The major product (45% yield) of the reaction is 4-trans-(2-olivetyl)pinene (IV),[11] $[\alpha]D$ −87° (CHCl₃); δ (CCl₄)[12] 0.88 (ω-methyl group), 0.96 and 1.32 (two bridge methyls), 1.88 (C-2 methyl), 3.98 (s, br, C-4 proton), 5.69 (s, br, C-3 proton), 6.10 (s, two aromatic protons).

The unstable, isomeric olivetyl pinene (V)[11] which is chromatographically more polar than IV was obtained in 20% yield; $[\alpha]D$ −48° (CHCl₃); δ (CCl₄) 0.88, 0.93, 1.29, and 1.82 (four methyl groups as in IV), 3.67 (C-4 proton), 5.68 (C-3 proton), 6.01 and 6.15 (two s, slightly split; aromatic protons). A stable diacetate could be prepared, $[\alpha]D$ −70° (CHCl₃).

Compound VI[11] is the least polar component of the reaction mixture (yield 15%), δ (CCl₄) 0.93 and 1.30 (four bridge methyl groups; the higher field signal overlaps the ω-methyl band), 1.85 (two olefinic methyl groups), 3.65 and 3.86 (br, s, two C-4 protons), 5.65 (two vinylic protons), 6.05 (s, one aromatic proton).

When rac-verbenol was used in the above-described reaction two of the reaction products were obtained in crystalline form, dl-IV,[11] mp 100–101°, and dl-VI,[11] mp 178–180°. The nmr and infrared spectra of these racemates were identical with those of the corresponding noncrystalline compounds obtained from (−)-verbenol.

Treatment of (−)-IV with boron trifluoride etherate in methylene chloride at room temperature for 10 min converted it in 85% yield into (−)-II (infrared, nmr, tlc identical with those of authentic material;[6] $[\alpha]D$ −250° (CHCl₃), indicating an optical purity of ca. 97%).

(−)-Δ¹⁽⁶⁾-THC (II), $[\alpha]D$ −245° (CHCl₃), could also be isolated directly in a 35% yield from the condensation of (−)-verbenol with olivetol when catalyzed by boron trifluoride etherate instead of p-toluenesulfonic acid.[13]

In the p-toluenesulfonic acid catalyzed condensation, only one 4-(2-olivetyl)pinene is observed, namely IV, which on isomerization yields trans-II exclusively. Since this transformation (IV → II) can hardly involve epimerization at C₄ or C₅, IV must possess the trans configuration. Similarly no cis-II was observed in the direct condensation, using boron trifluoride. The exclusive formation of trans-II and trans-IV is undoubtedly due to steric factors. These considerations make us assign a trans configuration also to compounds V and VI.

(−)-Δ¹⁽⁶⁾-THC was partly converted into (−)-Δ¹-THC by addition of hydrogen chloride to the double bond and subsequent elimination using the dehydrohalogenation procedure of Fahrenholtz, et al.[2c] Thus by passing dry hydrogen chloride through a solution of (−)-II in toluene at −15°, with zinc chloride as catalyst, compound VII was obtained (tlc, infrared, and nmr identical with those of racemic VII[2c]).[14] Boiling VII with sodium hydride in tetrahydrofuran[2c] gave a mixture of (−)-II and (−)-I, which were separated by careful chromatography on Florisil. (−)-Δ¹-Tetrahydrocannabinol (55% yield in the last two steps, on the basis of unrecovered (−)-II) thus obtained is identical with the natural product[4] (infrared, nmr, tlc, $[\alpha]D$ −152° (CHCl₃)).

After the present investigation had been completed we were informed by Dr. T. Petrzilka from Eidg. Technischen Hochschule that an unrelated synthesis of (−)-cannabidiol (III) had been achieved in Zurich.[7] In view of the known conversion of III into (−)-I[4] and (−)-II[5,6] the Swiss synthesis represents a further route to these compounds.

(8) Prepared from (−)-α-pinene, $[\alpha]D$ −51.5° (CHCl₃), according to Whitham.[9] The verbenol thus synthesized, $[\alpha]D$ −117° (CHCl₃), is a mixture of (−)-cis- and (−)-trans-verbenols.[10]

(9) G. Whitham, J. Chem. Soc., 2232 (1961).

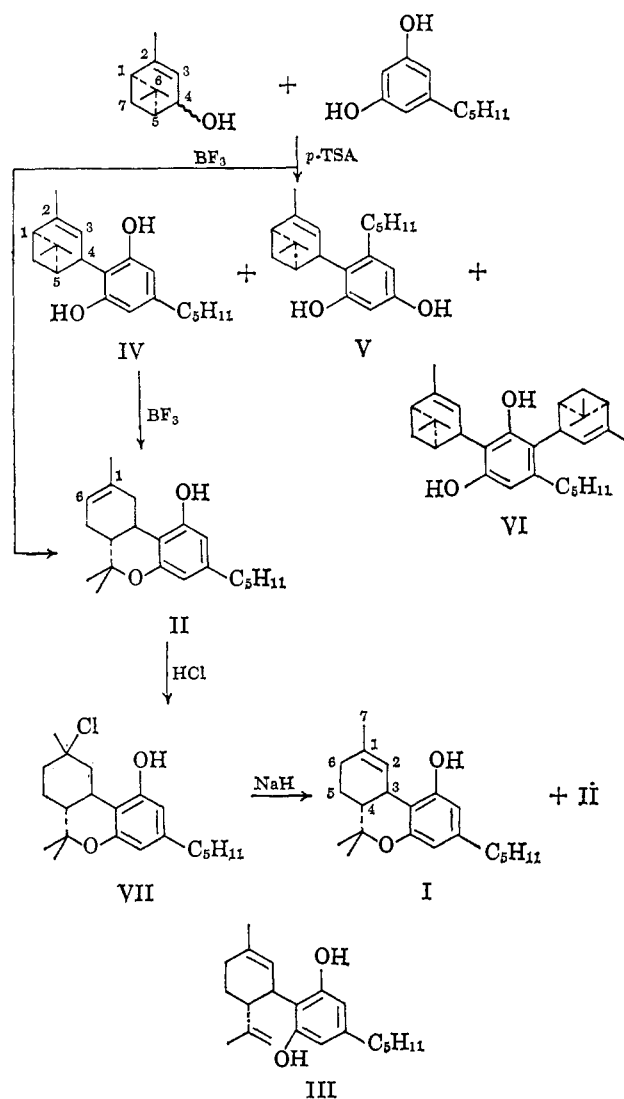(10) Y. Chretien-Bessière, Bull. Soc. Chim. France, 2182 (1964).

(11) Elemental analytical data in accord with theory were obtained for this substance. On tlc only one spot was observed.

(12) Values are given in parts per million. Letters denote broad (br), singlet (s).

(13) (+)-Δ¹⁽⁶⁾-THC, $[\alpha]D$ +248° (CHCl₃), was obtained by both the above procedures from (+)-verbenol. (+)-Δ¹⁽⁶⁾-THC showed no ataxia activity at the ED₅₀ level of the (−) modification.

(14) The optical activity of (−)-VII was not determined as the compound has so far resisted crystallization, and attempts at purification by chromatography on Florisil caused dehydrohalogenation, giving (−)-II in 90% yield. Distillation led to partially decomposed material.

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A General Naphthalene Synthesis, Illustrated with a Viable Preparation of Octamethylnaphthalene

Sir:

The distorted geometry of octamethylnaphthalene[1,2] suggests that it (and related compounds) may show unusual chemical behavior. Unfortunately the previous synthesis[3] is tedious and not amenable to the preparation of sufficient quantities for extensive studies. We now report a simple, high-yield synthesis of octamethylnaphthalene which also has the virtue of great generality for the synthesis of substituted naphthalenes and other ring structures.

Addition of benzyne[4] to the readily available[5] hexamethyl-2,4-cyclohexadienone furnished adduct I (R_1 = R_2 = H), mp 108–108.5°, in 73% yield. In a similar fashion, addition of 3,6-dimethylbenzyne (from 3,6-

I   II
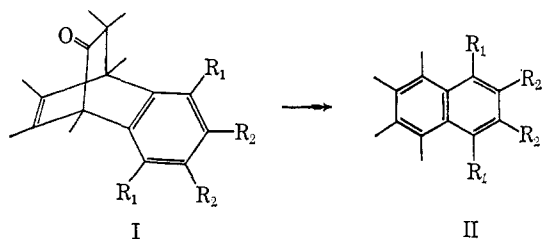
dimethylanthranilic acid) gave I (R_1 = CH_3; R_2 = H), mp 103–104°, and 4,5-dimethylbenzyne gave I (R_1 = H; R_2 = CH_3), mp 62–65°, each in 76% yield.[6,7]

The aryne adducts I were converted to the corresponding naphthalenes II by one of several routes. The most convenient is illustrated by the preparation of 1,2,3,4,5-8-hexamethylnaphthalene from I (R_1 = CH_3; R_2 = H) in 87% yield by reaction at 70° for 4.5 hr with dimsylsodium[8] in DMSO. The mechanism presumably involves the intermediate III; isobutyric acid was isolated and identified.[9]

(1) D. M. Donaldson and J. M. Robertson, *J. Chem. Soc.*, 17 (1953). There is some controversy regarding this early X-ray determination; see G. Gafner and F. H. Herbstein, *Nature*, 200, 130 (1963).

(2) For a stimulating review of *peri* interaction in naphthalenes, see V. Balasubramaniyan, *Chem. Rev.*, 66, 567 (1966).

(3) B. J. Abadir, J. W. Cook, and D. T. Gibson, *J. Chem. Soc.*, 8 (1953).

(4) L. Friedman and F. M. Logullo, *J. Am. Chem. Soc.*, 85, 1549 (1963); M. Stiles, R. G. Miller, and U. Burckhardt, *ibid.*, 85, 1792 (1963).

(5) H. Hart, P. M. Collins, and A. J. Waring, *ibid.*, 88, 1005 (1966).

(6) All new compounds gave satisfactory analyses and had infrared and nmr spectra consistent with the assigned structures.

(7) In the case of substituted benzynes, we used a modification of the published procedure, which gives improved yields. We are indebted to Professor Friedman for kindly communicating this procedure in advance of publication.

(8) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 87, 1345 (1965).

III

$$II + [(CH_3)_2C-\overset{\overset{O}{\|}}{C}-CH_2SOCH_3]$$

$$\downarrow$$

$$(CH_3)_2CHCO_2H + DMSO$$
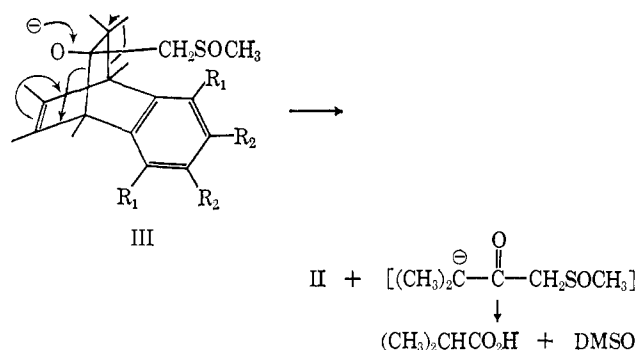
Alternatively, adducts I were reduced quantitatively with lithium aluminum hydride to a mixture of epimeric alcohols which, with NaH in DMSO, gave the corresponding naphthalene IV (and, presumably, isobutyraldehyde).
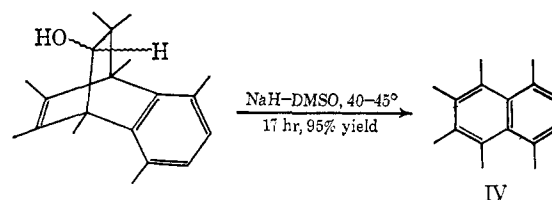
A third method for effecting the conversion of I → II is pyrolysis. I (R_1 = CH_3; R_2 = H) at 450° was converted to IV (17.8%), dimethylketene (17.9%, trapped as the anilide), and 80% of recovered I; undoubtedly a higher temperature would improve the conversion.

Octamethylnaphthalene was best prepared[10] from IV by bischloromethylation[11] and reduction (LiAlH₄), in over-all 71% yield, mp 179.5–181.0°; it had two equal singlets in the nmr, at τ 7.59 (1,4,5,8-CH_3) and 7.75 (2,3,6,7-CH_3).[12] Its ultraviolet spectrum agreed with that previously reported.[13]

Since the dienone and aryne components of this synthesis can be broadly selected, this method constitutes a versatile naphthalene synthesis; it should be capable of extension (*via* other arynes) to many ring systems. We are exploiting the method as well as the ground- and excited-state chemistry of octamethylnaphthalene.[14,15]

(9) The dimsylsodium need not be prepared directly; I (R_1 = CH_3; R_2 = H) with NaH in DMSO at 70–75° for 4 hr gave the corresponding II in 83% yield.

(10) Clearly octamethylnaphthalene could be produced directly if tetramethylbenzyne were used. However, the commercial availability of 4,7-dimethylisatin (Research Organic/Inorganic Chemical Co., Sun Valley, Calif.), the immediate precursor of 3,6-dimethylanthranilic acid, makes this benzyne somewhat easier to obtain than tetramethylbenzyne.

(11) This reaction goes in excellent yield directly to the bis(chloromethyl) product. It goes very poorly, however, with the isomeric 1,2,3,4,6,7-hexamethylnaphthalene; for similar difficulties in chloromethylating *peri* positions, see ref 3.

(12) Nmr spectra of 24 methylnaphthalenes have been studied by F. F-H. Yew, R. J. Kurland, and G. J. Mair, *Anal. Chem.*, 36, 843 (1964).

(13) H. Dannenberg and D. Dannenberg-von Dresler, *Chem. Ber.*, 89, 1326 (1956).

(14) For example, octamethylnaphthalene forms a deep blue complex with TCNE in benzene, chloroform, or *n*-hexane, the color of which is rapidly discharged with ethanol. Octamethylnaphthalene gives a Diels-Alder adduct with benzyne.

(15) We are grateful to the National Science Foundation for support of this research.

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