

temperature; GLC indicated no remaining neutralized substrate. After careful filtration, the ethanol was partially evaporated on a rotary vacuum apparatus, the residue taken up in methylene chloride and washed several times with water, and the organic solution dried over magnesium sulfate. After filtration and vacuum removal of solvent the residue was distilled bulb-to-bulb to give 2.1 g (60% yield) of distillate identical in spectral and GLC properties with authentic 2-methyl-6-(trifluoromethyl)aniline: bp 65 °C (5.3 mm), n_D^{21} 1.4822; $^1\text{H NMR}$ (CDCl_3) δ 2.1 (s, 3, ArCH_3), 4.05 (br, 2, NH_2), multiplets centered at 6.6 and 7.2 (3, Ar H).

Anal. Calcd for $\text{C}_8\text{H}_8\text{F}_3\text{N}$: C, 54.86; H, 4.60; N, 8.00. Found: C, 55.25; H, 4.65; N, 8.02.

(B) Reaction of 4g with Ethanol. In 150 mL of a 1.73 N sodium ethoxide (in ethanol) solution was added 25 g (0.1 mol) of solid salt 4g portionwise. Instant reaction occurred with precipitation of sodium chloride. The material was stirred at room temperature $1\frac{1}{2}$ h and then permitted to stand overnight. Mild cooling was necessary to maintain the temperature under 30 °C during salt addition. After filtration of solid through a coarse sintered glass filter, the filtrate was vacuum treated to remove most of the alcohol. The residue was treated with 300 mL of water and then washed twice with ether. The ether extracts were dried over magnesium sulfate, filtered, and vacuum treated to remove solvent to give 19.2 g crude aniline. This oil (18.7 g) was distilled by bulb-to-bulb distillation, with 15.2 g collected from an oven temperature of 120–135 °C (0.05–0.15 mm) (69% yield) of 2-(ethoxymethyl)-6-(trifluoromethyl)aniline: $^1\text{H NMR}$ (CDCl_3) δ 1.22 (t, $J = 7$ Hz, 3, CH_3CH_2), 3.50 (quartet, $J = 7$ Hz, 2, $\text{CH}_3\text{CH}_2\text{O}$), 4.50 (s, 2, ArCH_2O), (br, 2, NH_2), 6.65 (t, 1, Ar H), 7.1–7.75 (multiplets, 2, Ar H).

Anal. Calcd for $\text{C}_{20}\text{H}_{12}\text{F}_3\text{NO}$: N, 6.39. Found: N, 6.70.

(C) Preparation of 2-Methyl-6-(trifluoromethyl)aniline by Catalytic Hydrogenation from 4g. 4g (ca. 228 g from 1 mol of 1g, method B) was stirred with 800 mL of ethyl acetate and 1 L of aqueous 10% sodium carbonate solution. After layer separation the aqueous layer was washed with 200 mL of ethyl acetate, and the latter was combined with the organic phase in a 2-L pressure bottle containing 1 mol of triethylamine and 14.8 g of 5% Pd/C (containing 50% by wt water). This material was then hydrogenated over 2 h at 25–50 °C at 50 psi in a Parr shaker. The contents were filtered through clay and washed with 1 L water, with the latter washed with 200 mL of ethyl acetate. The combined organic layers were stripped of solvent on a rotary evaporator and the residue distilled at 20 mm to give, bp 65–70 °C, 96.5 g of 2-methyl-6-(trifluoromethyl)aniline (55% yield from 1g).

(D) Preparation of 2-Methyl-6-(trifluoromethyl)aniline by Hydrogenation of Quaternary Salt. The procedure for

preparing 4g, part B, was carried out to the point where 600 mL of solvent and water were distilled off rapidly. The clear, slightly yellow solution was then cooled to 40 °C, and 700 mL of ethylene dichloride was added followed by 90 g (1.5 equiv) of trimethylamine dissolved in methanol to a volume of ca. 130 mL. A mild exotherm occurred; the mixture was stirred for 20–30 min to insure complete reaction of amine. The solution was then heated to boiling and excess trimethylamine and methanol were removed by distillation. Precipitation of quaternary salt proceeded at 70–72 °C, preferably by seeding. Distillation was continued until a head temperature of 82 °C was reached. The mixture was then cooled to below 10 °C, filtered, and the salt-cake washed on the filter with fresh 1,2-dichloroethane. Yield of [2-amino-3-(trifluoromethyl)benzyl]trimethylammonium chloride after air-drying was 87% from 1g: mp 220–221 °C; $^1\text{H NMR}$ ($\text{Me}_2\text{SO}-d_6$) δ 3.20 (s, 9, CH_3), 5.0 (s, 2, CH_2), 6.2 (s (br), 2, NH_2), 6.8 (t, $J = 7$ Hz, 1, Ar H), 7.6 (d, $J = 7$ Hz, 2, Ar H).

Anal. Calcd for $\text{C}_{11}\text{H}_{16}\text{ClF}_3\text{N}_2$: C, 49.17; H, 6.00; N, 10.42; Cl, 13.29. Found: C, 49.13; H, 6.01; N, 10.37; Cl, 13.31.

The quaternary salt was dissolved in water to a concentration of 3 M and then shaken over ca. 10 g of 5% Pd/C (containing 50% weight water) under 60 psi of H_2 at 50 °C in a Parr shaker. After hydrogen uptake was complete in 2–3 h, the mixture was filtered and the two-phase filtrate separated by using ca. 200 mL of methylene chloride. The lower, organic layer was dried over MgSO_4 , filtered, and solvent distilled through a 10-in. Vigreux column. The residue was 2-methyl-6-(trifluoromethyl)aniline obtained in 99% assay and 97% yield from quaternary salt.

Registry No. 1a, 34774-84-0; 1b, 92643-44-2; 1c, 34774-86-2; 1d, 62926-90-3; 1e, 92643-45-3; 1f, 92643-46-4; 1g, 88301-96-6; 2a, 92643-47-5; 2b, 92643-48-6; 2c, 92643-49-7; 2d, 92643-50-0; 2e, 92643-51-1; 2f, 92643-52-2; 2g, 88301-75-1; 3g, 92643-53-3; 4a, 88301-81-9; 4b, 88301-76-2; 4c, 88301-77-3; 4d, 88301-78-4; 4e, 88301-79-5; 4f, 88301-80-8; 4g, 88301-74-0; a, 62-53-3; b, 578-54-1; c, 95-53-4; d, 90-04-0; e, 134-20-3; f, 51114-68-2; g, 88-17-5; Me_2S , 75-18-3; HCl, 7647-01-0; $\text{PhCH}_2\text{S}(\text{O})\text{Me}$, 824-86-2; PhCHO , 100-52-7; PhCH_2SMe , 766-92-7; $\text{MeO}-p\text{-C}_6\text{H}_4\text{S}(\text{O})\text{Me}$, 3517-99-5; $\text{MeO}-p\text{-C}_6\text{H}_4\text{CH}_2\text{Cl}$, 824-94-2; $\text{MeSCH}_2\text{-o-C}_6\text{H}_4\text{NHC}(\text{O})\text{CH}_3$, 65134-90-9; $\text{MeS}(\text{O})\text{CH}_2\text{-o-C}_6\text{H}_4\text{NHC}(\text{O})\text{CH}_3$, 92643-54-4; $\text{AcNH-o-C}_6\text{H}_4\text{CHO}$, 13493-47-5; $\text{ClCH}_2\text{C}(\text{O})\text{Cl}$, 79-04-9; AcCl , 75-36-5; 2-chloro-2'-[(methylthio)methyl]-6'-methoxyacetanilide, 92643-55-5; 2-chloro-2'-[(methylsulfinyl)methyl]-6'-methoxyacetanilide, 92643-56-6; 2-chloro-2'-formyl-6'-methoxyacetanilide, 92643-57-7; 2-(chloromethyl)-6'-(trifluoromethyl)acetanilide, 88301-82-0; 2-methyl-6-(trifluoromethyl)aniline, 88301-98-8; 2-(ethoxymethyl)-6-(trifluoromethyl)aniline, 92643-58-8; [2-amino-3-(trifluoromethyl)benzyl]trimethylammonium chloride, 88301-97-7.

Notes

Divinorin A, a Psychotropic Terpenoid, and Divinorin B from the Hallucinogenic Mexican Mint *Salvia divinorum*

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While nonalkaloidal constituents have been implicated as being at least partially responsible for the biological

activity of several hallucinogenic plants,² little has been reported on the structures of such possible hallucinogens. The Mexican labiate *Salvia divinorum* (Epling and Jativa-M.) is used in divinatory rites by the Mazatec Indians of Oaxaca, Mexico. An infusion prepared from the crushed fresh leaves of this plant (known locally as *ska Maria Pastora*) is used to induce "visions" and its psychotropic effects have been verified by a number of researchers.³

(1) Address correspondence to this author at the Department of Chemistry.

(2) (a) Shultes, R. E.; Hofmann, A. "The Botany and Chemistry of Hallucinogens"; Charles C. Thomas Publisher: Springfield, IL, 1980; 2nd ed. (b) Lewis, W. H.; Elvin-Lewis, M. P. F. In "Medical Botany"; Wiley: New York, 1977; Chapter 18. (c) Diaz, J. L. *Ann. Rev. Pharmacol. Toxicol.* 1977, 17, 647.

*School of Pharmacy.

†Department of Chemistry.

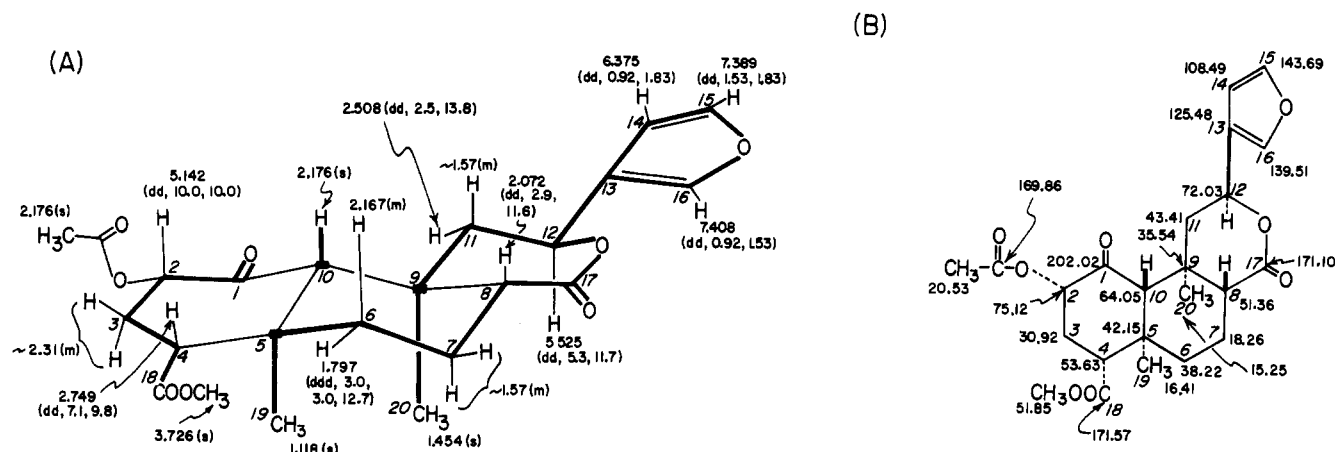


Figure 1. Divinorin A (1): (A) 360-MHz ¹H NMR data in CDCl₃, δ values from (CH₃)₄Si [multiplicity and *J* values (in Hz) in parentheses]; (B) 90.56-MHz ¹³C NMR data in CDCl₃, δ values from (CH₃)₄Si; assignments are based on off-resonance, selective, and gated-selective decoupling experiments and chemical shift comparisons with compounds 2-4 and model compounds.

Furthermore, upon administration of large doses of the plant extract in animals, one observes behavioral patterns that resemble the "intoxication" the infusion produces in human beings. Despite previous investigations, the principle(s) responsible for this biological activity has never been identified.⁴ We now report the isolation and the structures of the new neoclerodane diterpenes, divinorins A and B from *S. divinorum*. Divinorin A, the first clearly documented psychotropic terpenoid,⁵ exerts a sedative effect on mice when tested in a bioassay based on a modification of Hall's open field.⁶

Lyophilized, pulverized leaves (5.35 kg) of *S. divinorum* were extracted with ether. The nonpolar components were removed from the concentrated extract through partition between hexanes and 90% aqueous methanol. The dried methanolic fraction was crudely purified by silica gel flash column chromatography⁷ (hexanes-ethyl acetate, 2/1). Further purification of the combined biologically active fractions by additional silica gel flash column chromatography (methylene chloride-methanol, 20/1) followed by repeated recrystallization yielded pure divinorins A (1) (1.2 g) and B (3) (50 mg).⁸

(3) (a) Wasson, R. G. *Bot. Mus. Leaflet*, Harvard Univ. 1962, 20, 77. (b) Hofmann, A. "LSD: My Problem Child"; McGraw-Hill: New York, 1980; pp 127-144. (c) Valdes, L. J.; Diaz, J. L.; Paul, A. G. *J. Ethnopharmacol.* 1983, 7, 287.

(4) (a) Hofmann, A. *Planta Medica* 1964, 12, 341. (b) Diaz, J. L. In "Etnofarmacologia de Plantas Alucinogenas Latinoamericanas"; Diaz, J. L., Ed.; Centro Mexicano de Estudios en Farmaco-dependencia: Mexico City, 1975; pp 149-152. Although it was reported that active fractions reacted with Ludy Tenger reagent (a modified Dragendorff's reagent) and possibly alkaloids, extensive work in our laboratory has shown that the pharmacologically active extracts from *S. divinorum* do not contain alkaloids, nor were we able to isolate any alkaloids from the plant itself.

(5) Infusions and tinctures of the green matter from *Lagochilus inebrians* Bge. are described as having pharmacological activity exhibited by hemostatic and sedative properties of a general nature that are in part attributed to the spiro ether-containing labdane, lagochilin, which has been isolated from the plant. However, details regarding activities of the preparations and the diterpene itself are not available: (a) Abramov, M. M.; Yaparova, S. A. *J. Appl. Chem., USSR* 1963, 36, 2471. (b) Chizhov, O. S.; Kessenikh, A. V.; Yakolev, I. P.; Zolotarev, B. M.; Petukhov, V. A. *Tetrahedron Lett.* 1969, 1361.

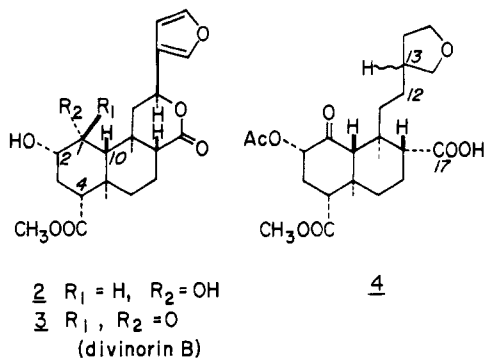
(6) Brimblecombe, R. W.; Green, A. L. *Nature (London)* 1962, 194, 983. The following is a summary of our modified bioassay: Mice were dosed with various fractions of the extract and the animals' activities were observed in the field, which consisted of a 3-ft. circle divided into squares. Parameters measured were the numbers of squares entered (lines crossed), rearings on the hind legs, and time spent immobile. Divinorin A reduced all three measures of activity, resembling that of *S. divinorum* in human beings.^{2c}

(7) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* 1978, 43, 2923.

Divinorin A (1), mp 242-244 °C, [α]_D²⁵ -45.3° (c 8.530, CHCl₃), had the molecular formula C₂₃H₂₈O₈. The UV spectrum [211 nm (ε 5260)] was indicative of the presence of the furan moiety. This was further corroborated by the products from the hydrogenation reaction of divinorin A which was accompanied by hydrogenolysis at C-12. Thus, catalytic hydrogenation of divinorin A in methanol over 5% Pd/C provided quantitatively a stereoisomeric mixture (at C-13) of hexahydro derivatives 4. Although it was difficult to determine the presence of a ketone group from the IR spectrum of divinorin A alone, as its carbonyl region is strongly absorbed due to three other carbonyl functionalities, the presence of a highly hindered ketone group in divinorin A became evident from the results of its sodium borohydride reduction. The sodium borohydride reduction of divinorin A was found to be extremely sluggish at room temperature, presumably owing to the severe steric crowding near the ketone located at C-1. However, reduction at higher temperatures produced the mixture of 2 (40%) and its stereoisomeric diol (40%). The latter appears to be stereoisomeric at C-8 and/or C-9, which evidently had resulted from its "base-promoted" C-8/C-9 cleavage followed by reclosure prior to the reduction. The stereochemistry of the diol 2 was secured as identical with that of divinorin A by its conversion to the latter via acetylation with acetic anhydride/pyridine, at room temperature, followed by oxidation with pyridinium chlorochromate. In contrast, the same sequence of the reactions of the other diol gave a thus far undetermined stereoisomer of divinorin A.

Both ¹H and ¹³C NMR spectra were particularly informative since all ¹H and ¹³C signals could be observed and assigned through extensive proton decoupling, off-resonance decoupling, and selective decoupling experiments. These provided partial structures which are indicated in connecting thick lines and by solid blocks denoting quaternary carbons in Figure 1A. The linkage between C-1 and C-10 was ascertained from the ¹H NMR spectrum in acetone-*d*₆ of the diol 2, mp 218-220 °C, ob-

(8) Purified, recrystallized divinorin A has activity slightly stronger than the original plant extract, whereas divinorin B was inactive in this bioassay (this does not preclude the possibility of a different psychotropic activity in the latter). The mother liquor from recrystallization contains at least two more terpenoids in addition to these two divinorins. This mixture shows substantially stronger activity, thus suggesting the presence of a minor component(s) that either synergistically enhances the activity of divinorin A or has strong sedative properties in itself. Isolation of these minor components and identifying their activities is currently being pursued.



tained in 40% yield from divinorin A with sodium borohydride in isopropyl alcohol at 35 °C for 2.5 h. Thus, inspection of the coupling constants involving protons at C-10, C-1, and C-4 ($J_{10\beta,1\beta} = 2.0$ Hz, $J_{1\beta,2\beta} = 2.1$ Hz, $J_{2\beta,3\beta} = 4.9$ Hz, $J_{2\beta,3\alpha} = 11.4$ Hz, $J_{3\beta,4\beta} = 2.1$ Hz, and $J_{3\alpha,4\beta} = 13.2$ Hz) led to the proposed structure 1 for divinorin A.

This structure was finally confirmed by a single-crystal X-ray diffraction experiment. A perspective drawing of the final X-ray model, less hydrogen atoms, is shown in Figure 2. Details of the X-ray analysis are given in the Experimental Section and bond lengths, angles, other crystallographic parameters are provided as supplementary information.

Divinorin B (3), mp 213–216 °C, $[\alpha]^{22}_D -3.39^\circ$ (c 0.441, EtOH), was found to be desacetyldivinorin A, which was verified by its conversion into divinorin A via acetylation with acetic anhydride in pyridine. The absolute configurations are proposed based on the CD spectra (MeOH) of divinorins A (1) ($\Delta\epsilon_{294} -2.63$) and B (3) ($\Delta\epsilon_{290} -1.41$) and hexahydrodivinorin A (4) ($\Delta\epsilon_{295} -1.67$). While the absolute configurations shown appear to be corroborated by the negative $n \rightarrow \pi^*$ Cotton effect of isofructicolone,⁹ the unambiguous assignment of the absolute configurations of the divinorins is yet to be made.

Experimental Section

Microanalysis was performed by Spang Microanalytical Laboratory, Eagle Harbor, MI. Melting points were taken on a Fisher Johns melting point apparatus and are uncorrected. The ultraviolet spectrum was determined on a Hewlett-Packard 8450A UV/vis spectrophotometer. Infrared spectra were recorded on a Perkin-Elmer Model 281 spectrometer as potassium bromide (KBr) disks. Mass spectra were taken with a Finnigan Model 4023 GC/MS spectrometer. Nuclear magnetic resonance spectra were obtained on a Bruker WM360 spectrometer (360 MHz for 1H and 90.56 MHz for ^{13}C) in $CDCl_3$ unless otherwise stated and all chemical shifts are reported in parts per million relative to internal tetramethylsilane. Optical rotations were determined on a Perkin-Elmer 241 polarimeter using a quartz cell of 10-cm length and 1-mL volume. Circular dichroism spectra were recorded on a JASCO J-40A automatic recording spectropolarimeter using a quartz cell of 20-mm length and 3.5-mL volume.

Collection, Extraction, and Isolation. Live specimens of *S. divinorum* were collected at Cerro Quemado (Sept 3, 1979) and Cerro Rabon (March 7, 1980) in Oaxaca, Mexico. The plants were cultivated at the Matthaei Botanical Gardens, The University of Michigan, in order to provide material for research.

Fresh *Salvia* leaves (5.350 kg) were lyophilized and forced through 7- and 16-mesh screens yielding 674.1 g of powdered dry material. The powder was extracted in 30–40-g lots for 24 h with ethyl ether (1 L/lot) using a Soxhlet apparatus and dried in vacuo, giving a total of 27.51 g of ether extract. The extract was partitioned between hexanes (600 mL) and 90% aqueous methanol (600 mL) for 48 h using a liquid/liquid extractor and yielded, after

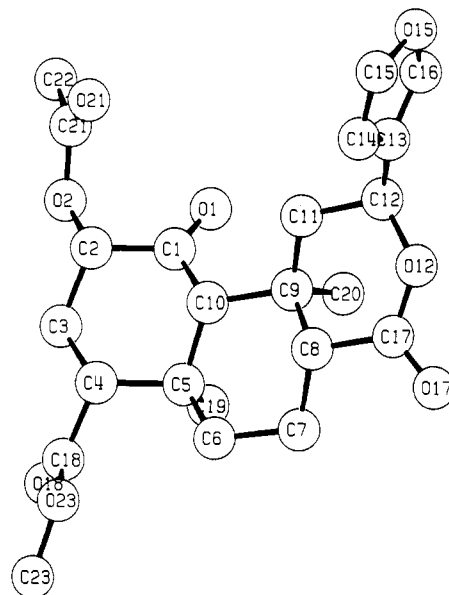


Figure 2. Computer-generated perspective drawing of divinorin A (1) with crystallographic numbering scheme.

removal of the solvent in vacuo, a 7.41-g methanol fraction. The hexane fraction was repartitioned as above and the combined concentrated methanol fractions (9.36 g) were subjected to further purification by flash column chromatography.

In a typical experiment, a Fischer Porter 2.5 × 25 cm column containing 55 g of silica gel (70–230 mesh), which had been treated with 2.75 mL of water, was equilibrated with the eluting solvent, hexanes/ethyl acetate (2/1). Fivehundred milligrams of the methanolic fraction was adsorbed on 5 g of silica gel and carefully poured on the preequilibrated column. The eluting solvent was then forced (using nitrogen pressure) through the column at the flow rate of 25–35 mL/min and 100-mL fractions were collected. Each fraction was followed by bioassay, and fractions 4–9 were determined to be active. The 9.36 g of methanolic fraction yielded 2.349 g of desired crude material. The material recovered was further purified by using another flash column chromatography. Fivehundred milligrams of the crudely purified methanol fraction, adsorbed on 5 g of silica gel, was added to the top of the 2.5 × 25 cm Fischer Porter column containing 55 g of silica gel which had been treated with 2.75 mL of water and preequilibrated with the eluting solvent, methylene chloride/methanol (20/1). The column was eluted at a rate of 25–35 mL/min with the aid of 5 psi of nitrogen pressure, and 25-mL fractions were collected. The biologically active fractions (fractions 3–5) were combined. The 2.349 g of starting material gave 1.515 g of impure diterpene mixture from which pure divinorin A (893 mg) was obtained after two recrystallizations from absolute ethanol. The combined mother liquors were subjected to preparative TLC purification (Merck GF-254, 15 × 1 mm plate, 20 × 20 cm, developed with $CHCl_3/MeOH/H_2O$, 100/10/1), which gave more divinorin A (305 mg; R_f 0.63) and crude divinorin B. The crude divinorin B was further purified by two recrystallizations from methanol, yielding 50 mg of divinorin B (R_f 0.48). **Divinorin A (1):** mp 242–244 °C; $[\alpha]^{22}_D -45.3^\circ$ (c 8.530, $CHCl_3$); UV (MeOH) 211 nm (ϵ 5260); IR (KBr) 3220, 1745, 1735, 1240, 875 cm^{-1} ; NMR (1H and ^{13}C) see Figure 1; mass spectrum (EI; 70 eV), m/z 432 (M^+ , 1.5), 273 (6.5), 166 (8.6), 121 (13.0), 108 (8.0), 107 (9.7), 95 (17.9), 94 (100), 93 (9.9), 91 (6.9), 81 (11.2), 79 (5.5), 55 (13.7); CD (MeOH) $\Delta\epsilon_{294} -2.63$. Anal. Calcd for $C_{23}H_{28}O_8$: C, 63.89; H, 6.48; O, 29.63. Found: C, 63.44; H, 6.61; O, 30.14. **Divinorin B (3):** mp 213–216 °C; $[\alpha]^{22}_D -3.39^\circ$ (c 0.441, EtOH); IR (KBr) 3495, 3140, 1735, 1715, 1250, 860 cm^{-1} ; 1H NMR (360 MHz) δ 1.101 (s, 3 H, 19-H), 1.484 (s, 3 H, 20-H), 1.50–1.65 (m, 3 H, 7-H's and 11 β -H), 1.797 (ddd, 1 H, $J = 2.7, 3.1, 12.9$ Hz, 6 α -H), 2.020 (ddd, 1 H, $J = 11.4, 13.5, 13.6$ Hz, 3 α -H), 2.074 (dd, 1 H, $J = 2.0, 11.7$ Hz, 8-H), 2.169 (s, 1 H, 10-H), 2.17 (m, 1 H, 6 β -H), 2.480 (ddd, 1 H, $J = 3.1, 7.7, 13.6$ Hz, 3 β -H), 2.548 (dd, 1 H, $J = 5.2, 13.4$ Hz, 11 α -H), 2.709 (dd, 1 H, $J = 3.1, 13.5, 4$ -H), 3.599 (d, 1 H, $J = 3.3$ Hz, OH), 3.717 (s, 3 H, COOMe), 4.080 (ddd, 1 H, $J = 3.3, 7.7, 11.4$ Hz, 2-H), 5.567

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(dd, 1 H, $J = 5.1, 11.7$ Hz, 12-H), 6.376 (dd, 1 H, $J = 0.92, 1.8$ Hz, 14-H), 7.399 (dd, 1 H, $J = 1.5, 1.8$ Hz, 15-H), 7.416 (dd, 1 H, $J = 0.92, 1.5$ Hz, 16-H); ^{13}C NMR ($\text{C}_6\text{D}_6\text{N}$; 90.56 MHz) δ 15.35 (q), 16.49 (q), 18.89 (t), 35.82 (t), 38.31 (s), 42.44 (s), 43.53 (t), 51.22 (d), 51.51 (q), 53.62 (d), 63.18 (d), 71.99 (d), 75.27 (d), 109.31 (d), 126.64 (s), 140.26 (d), 144.15 (d), 171.38 (s), 172.59 (s), 209.79 (s) ppm; CD (MeOH) $\Delta\epsilon_{290} -1.41$.

Hexahydrodivinorin A (4). A mixture of 150 mg of divinorin A (1) in 100 mL of methanol and 162 mg of 5% palladium on charcoal in a 125-mL round bottomed flask was hydrogenated at room temperature under a slightly positive pressure for 24 h. The catalyst was removed by filtration and the solvent removed in vacuo. The residual oil was dissolved in 25 mL of methylene chloride and extracted 3 times with 5-mL portions of 1% NaHCO_3 in H_2O . The combined aqueous layers were acidified to pH 1.0 with concentrated HCl and extracted 3 times with 5-mL portions of methylene chloride. The organic fraction was taken to dryness in vacuo and the crude oily product was recrystallized from ethanol-water to provide pure hexahydrodivinorin A (4) (143 mg): mp 196–198 °C; IR (KBr) 3100, 1755, 1735, 1725, 1225 cm^{-1} ; ^1H NMR (360 MHz) δ 1.033 (s, 3 H), 1.340 and 1.345 (both s, total 3 H), 2.137 and 2.139 (both s, total 3 H), 3.686 (s, 3 H); ^{13}C NMR (90.56 MHz) δ 15.99 (q), 19.71/19.74* (q), 20.48 (q), 21.26 (t), 27.19/27.27* (t), 31.33 (t), 32.10/32.22* (t), 38.10 and 38.29 (multiplicities not certain due to overlap), 38.19 (s), 38.37 (t), 39.56/39.63* (d), 42.91*/42.92 (s), 49.05*/49.08 (d), 51.71 (q), 54.02*/54.15 (d), 58.67*/58.79 (d), 67.84 (t), 73.31*/73.37 (t), 75.44*/75.45 (d), 169.61 (s), 171.65 (s), 177.26*/177.49 (s), 202.08/202.10* (s) (the paired chemical shifts represent those of spectroscopically resolved diastereomers, and the ones with asterisks indicate the more intense ^{13}C peaks between the two paired); mass spectrum (CI; CH_4), m/z (relative intensity) 467 (12), 440 (22), 439 ($\text{M} + \text{H}^+$; 100); 437 (11), 422 (15), 421 (68), 167 (6), 104 (17), 99 (8), 97 (6), 95 (7), 85 (9); CD (MeOH) $\Delta\epsilon_{296} -1.67$.

Sodium Borohydride Reduction of Divinorin A. Divinorin A (1; 260 mg) was dissolved in 120 mL of isopropyl alcohol in a 200-mL round bottomed flask and was treated with 14 mg of sodium borohydride. The mixture was warmed up to 33–35 °C and was kept at that temperature for 2.5 h. The reaction was terminated by addition of 3 mL of methanol. The solvent was removed under vacuum and the dried crude products were redissolved in 50 mL of chloroform and washed with 50 mL of 1% HCl and twice with 50-mL portions of water. The organic fraction was dried over sodium sulfate and taken to dryness (255 mg). The crude mixture was purified through flash column chromatography on silica gel (230–400 mesh; 30 g) using hexanes/ethyl acetate (1/2) as the eluting solvents. The more polar diol (2; 124 mg) was recovered along with the less polar, thus far unidentified stereoisomeric diol (120 mg; mp 234–235 °C). **Diol 2:** mp 218–220 °C; $[\alpha]_D^{25} +1.16^\circ$ (c 1.55, EtOH); IR (KBr) 3505, 1725, 1705 cm^{-1} ; ^1H NMR (acetone- d_6 ; 360 MHz) δ 1.163 (s, 1 H, 10-H), 1.375 (s, 3 H), 1.438 (s, 3 H), 1.56–1.62 (m, 4 H, 3 β -H, 6-H's and 7 α -H), 1.799 (dd, 1 H, $J = 11.9, 13.2$ Hz, 11 β -H), 1.964 (dddd, 1 H, $J = 3.3, 3.3, 3.5, 13.8$ Hz, 7 β -H), 2.109 (ddd, 1 H, $J = 11.4, 12.7, 13.2$ Hz, 3 α -H), 2.203 (dd, 1 H, $J = 2.1, 13.2$ Hz, 4-H), 2.294 (dd, 1 H, $J = 3.3, 12.3$ Hz, 8-H), 2.494 (dd, 1 H, $J = 5.6, 13.2$ Hz, 11 α -H), 3.358 (br s, 1 H, 1-OH), 3.553 (dddd, 1 H, $J = 2.0, 4.9, 5.4, 11.4$ Hz, 2-H), 3.623 (s, 3 H, COOMe), 4.027 (d, 1 H, $J = 5.4$ Hz, 2-OH), 4.207 (br s, 1 H, 1-H), 5.594 (dd, 1 H, $J = 5.6, 11.9$ Hz, 12-H), 6.593 (dd, 1 H, $J = 0.7, 1.8$ Hz, 14-H), 7.556 (dd, 1 H, $J = 1.6, 1.8$ Hz, 15-H), 7.650 (dd, 1 H, $J = 0.7, 1.6$ Hz, 16-H); ^{13}C NMR (acetone- d_6 ; 90.56 MHz) δ 17.02 (q), 18.07 (q), 19.71 (t), 29.39 (t), 37.39 (s), 38.50 (s), 41.22 (t), 44.75 (t), 51.24 (q), 52.79 (d), 55.81 (d), 56.05 (d), 69.69 (d), 72.12 (d), 72.33 (d), 109.70 (d), 127.74 (s), 140.62 (d), 144.52 (d), 172.12 (s), 173.75 (s); mass spectrum (CI; CH_4), m/z (relative intensity) 421 (7), 394 (21), 393 ($\text{M} + \text{H}^+$; 100), 375 (74), 357 (78), 343 (87).

Conversion of Diol 3 to Divinorin A (1). The diol 3 (25 mg) was dissolved in 7 mL of dry pyridine, placed in a 25-mL round bottomed flask, and treated with 1 mL of acetic anhydride. After being stirred at room temperature for 5 h, the reaction was terminated by addition of 1 mL of methanol. The mixture was poured into ice water (50 mL), its pH was adjusted to ~ 10 by addition of aqueous NH_4OH and it was extracted twice with 60-mL portions of chloroform. The combined organic layers were washed with 25 mL of 10% aqueous HCl and then 25 mL of water,

dried over sodium sulfate, and evaporated in vacuo. The crude mixture (35 mg) was purified via flash column chromatography (50 g of 230–400 mesh silica gel; eluted with hexanes/ethyl acetate (1/1)), providing 21 mg of diol 3 2-monoacetate along with 2 mg of the starting diol 3. **Diol 3 2-monoacetate:** IR (KBr) 3600, 1740, 1735, 1240 cm^{-1} ; ^1H NMR (360 MHz) δ 1.002 (s, 1 H, 10-H), 1.390 (s, 3 H), 1.458 (s, 3 H), 2.096 (s, 3 H, OAc), 3.677 (s, 3 H, COOMe), 4.292 (br s, 1 H, 1-H), 4.696 (ddd, 1 H, $J = 3.2, 4.6, 11.7$ Hz, 3-H); ^{13}C NMR (90.56 MHz) δ 16.81, 17.90, 18.72, 21.07, 24.90, 36.96, 37.87, 40.66, 51.43, 52.58, 55.00, 55.88, 67.36, 71.75, 74.60, 108.47, 125.91, 139.39, 143.78, 169.61, 171.68, 172.44.

The diol 3 2-monoacetate (19 mg), dissolved in 5 mL of methylene chloride, was placed in a 25-mL round bottomed flask and treated with 53 mg of PCC in 5 mL of methylene chloride at room temperature. After 30 h, the reaction mixture was diluted with 50 mL of ether. The ether layer was recovered by decantation and the dark residue was extracted with 10 mL of ether. The combined ether layers were dried over sodium sulfate and the organic solvents removed in vacuo. The crude reaction products (20 mg) were purified via flash column chromatography (55 g of Merck silica gel, 230–400 mesh; eluted with hexane/EtOAc (3/2) which yielded 10 mg of divinorin A (1) and 5 mg of diol 3 2-monoacetate.

Acetylation of Divinorin B (2). Divinorin B (10 mg) dissolved in 5 mL of dry pyridine and placed in a 10-mL round bottomed flask, was treated with 0.5 mL of acetic anhydride at room temperature. The mixture was stirred for 6 h at that temperature. The reaction was terminated by addition of 1 mL of methanol and the mixture poured into ice water (50 mL). The resulting precipitates were collected by filtration, washed thoroughly with water, and dried in vacuo. The crude product was recrystallized from absolute ethanol and found identical with divinorin A.

X-ray Crystallographic Analysis of Divinorin A (1). Crystals of divinorin A were obtained by slow cooling of a saturated ethanolic solution. A crystal of dimensions $0.078 \times 0.269 \times 0.418$ mm was mounted on a Syntex P2₁ diffractometer and found to have the space group $P2_12_12_1$ with $a = 6.369$ (2) Å, $b = 11.366$ (4) Å, and $c = 30.747$ (12) Å. The density was calculated to be 1.29 g/cc for $Z = 4$. Intensity data were obtained using Mo $K\alpha$ radiation monochromatized by means of a graphite crystal whose diffraction vector was perpendicular to the diffraction vector of the sample. A total of 2494 reflections with $2\theta < 50^\circ$ were measured, of which 1376 were considered observed [$I > 3\sigma(I)$]. The data were reduced by procedures previously used.¹⁰ The structure was solved using MULTAN78. Hydrogen atomic positions were calculated and added to the structure. They were given isotropic temperature factors one unit greater than the atom to which they are attached and their positions were not refined. Standard techniques were used to refine the structure to $R_1 = 0.087$ and $R_2 = 0.092$.

Note Added in Proof. After the original submission of the manuscript, we learned that Ortega et al. reported the structure of salvinorin which is identical with that of divinorin A described herein (Ortega, A.; Blount, J. F.; Manchand, P. S. *J. Chem. Soc., Perkin Trans. 1* 1982, 2505). Therefore, divinorins A and B should be called salvinorins A and B, respectively.

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Registry No. 1, 83729-01-5; 2, 92545-29-4; 3, 92545-30-7; 4, 92545-31-8.

Supplementary Material Available: Final positional parameters with estimated standard derivations are shown in Table I; anisotropic thermal parameters with their standard deviations

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are listed in Table II; Table III lists the crystallographically determined bond distances and angles (Tables I-II) (listings of observed and calculated structure factors amplitudes are available from the authors); a figure which shows a computer-generated stereodrawing with anisotropic thermal ellipsoids of the compound (5 pages). Ordering information is given on any current masthead page.

Preparation of α -Fluoro Enolates and Their Use in the Directed Aldol Reaction

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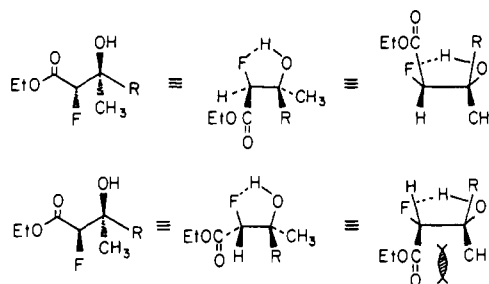
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Although the directed aldol reaction has been the subject of much investigation,¹ surprisingly little has been reported about the stereochemistry of α -heteroatom substituted enolates and their utilization in directed aldol reactions. The stereoselective formation of olefins by the aldol products of silyl-substituted enolates² on warming has engendered speculation that formation of the aldol product is itself diastereoselective.^{2d} Stereoselectively formed α -amino enolates^{1a,3} may react with high diastereoselectivity.⁴ In contrast, neither the stereochemistry of monohalogenated enolates⁵ nor their diastereoselectivity in aldol reactions has been reported.

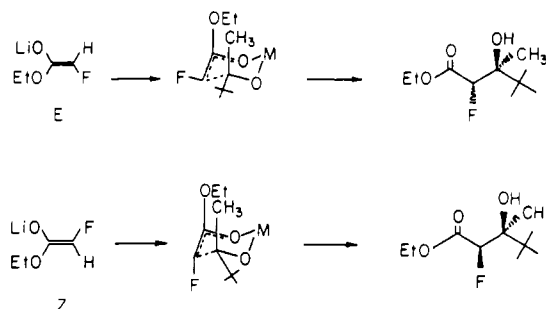
Results and Discussion

We have found that the lithium enolate of ethyl fluoroacetate may be readily prepared and efficiently utilized in the directed aldol reaction⁶ (Table I). The utility of the fluoroacetate residue in compounds such as γ -fluoroglutamic acid or fluorocitric acid in discerning biochemical pathways has been limited by the difficulty of constructing the fluorinated molecules. We are currently exploring the use of this anion in the stereoselective synthesis of such specifically fluorinated natural products, where substitution by fluorine has a little steric effect but a pronounced electronic effect on the properties of the molecule. Much early work has been reported on the use of ethyl fluoroacetate in synthesis but with no indication of stereochemistry and often under conditions where the fluorohydrin would not survive.⁷ Previously ethyl bromofluoroacetate,

Scheme I

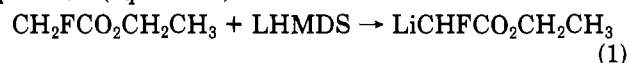


Scheme II



in a Reformatsky reaction, and the lithium enolate of *tert*-butyl fluoroacetate were used in the preparation of fluorocitrate⁸ and fluorohomocitric acid,⁹ respectively. In both reports, difficulty in the preparation of the lithium enolate of ethyl fluoroacetate or very low yields in the attempted directed aldol reaction of the lithium enolate were described. For the introduction of the fluoroacetate residue, commercially available ethyl fluoroacetate where the ester function can be easily manipulated further is the reagent of choice.

In contrast to the low yields of aldol product reported upon enolate formation with lithium diisopropylamide (LDA) at -78°C in the presence of 1 equiv of hexamethylphosphoric triamide (HMPA), generation of the enolate with lithium hexamethyldisilazide (LHMDS) at -78°C resulted in consistently higher yields of aldol products (eq 1 and 2). Furthermore it was observed that



generation of the base with methyllithium-lithium bromide complex in diethyl ether resulted in higher yields than when the base was isolated in the conventional manner.¹⁰ Success in the generation of the enolate with LHMDS led to our reexamination of the reaction with LDA. Comparable yields of aldol products were isolated when the enolate was formed with LDA at -105°C in the presence of HMPA. The enolate may be trapped with chlorotrimethylsilane to form the corresponding silyl enol ether (eq 3). The ratio of the *E*:*Z* enolate was found to be 1:1 by $\text{LiCHF}\text{CO}_2\text{CH}_2\text{CH}_3 + (\text{CH}_3)_3\text{SiCl} \rightarrow$



¹H NMR spectroscopy.¹¹ Not unexpectedly, the enol silyl ether-fluoroketene acetal was observed to decompose

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(11) Chemical shifts are reported in ppm from Me_4Si in carbon tetrachloride solution: 6.2, $J_{\text{H,F}} = 77$ Hz; 6.32, $J_{\text{H,F}} = 74$ Hz.