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FORMAL TOTAL SYNTHESIS OF β-PIPITZOL

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Abstract.- (±)-O-methylperezone (1b) was obtained by selective oxidative demethylation of (±)-leucoperezone trimethyl ether (4a). Compound (4a) was prepared by condensation of 2,3,5-trimethoxytoluene (5e) with 6-methyl-5-hepten-2-one, followed by reductive removal of the tertiary alcohol. The aromatic precursor 5e was prepared in four steps from 2,3-dimethoxytoluene (5a) and, alternatively, in three steps from 5-bromoveratraldehyde (6a). Racemic 1b and 4a were directly compared with the optically active molecules prepared from natural R(-)-perezone (1a).

We have recently shown[1] that the transformation[2,3] of perezone (1a) into the mixture of α-(2b) and β-pipitzol (3) can be stereocontrolled in any desired direction depending on the substrate and the reaction conditions. Thus, when perezone (1a) is treated[4] with boron trifluoride, the predominant reaction product is α-pipitzol (2b). Alternatively treatment[1] of O-methylperezone (1b) with aluminum trichloride in the presence of diethyl sulfide provides preferentially the β-isomer 3.

Syntheses[5] of α-cedrene (2a), possessing the stereochemistry of the widely distributed cedranolides[6] such as α-pipitzol (2b), are available. However no synthetic route to the less common β-pipitzol type[7] tricyclic sesquiterpenes appears to be known at present. Thus, if one would be able to prepare O-methylperezone (1b), a formal total synthetic route leading to β-pipitzol (3) can be completed.

The present work describes the synthesis of O-methylperezone (1b) by selective silver(II)oxide[8] demethylation of the phenolic ether 4a, which in turn was constructed[9] by condensation of 2,3,5-trimethoxytoluene 5e with commercially available 6-methyl-5-hepten-2-one, followed by removal of the tertiary alcohol. The aromatic precursor 5e was synthetized by two alternate routes starting from commercially available 5-bromovanillin in one case, and from 3-methylveratrole (5a) in the other case.

RESULTS AND DISCUSSION

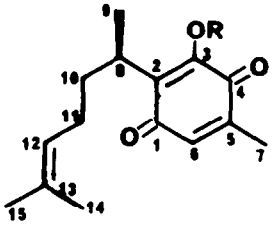
Nitration[10] of 3-methylveratrole (5a) in concentrated nitric acid at -10°C smoothly gave 5-nitro-2,3-dimethoxytoluene (5b) in 82% yield. The nitro group in 5b was straighforward converted to a methoxyl group as in 5e, through catalytic reduction to the amino group followed by diazoation to phenol (5d) and methylation. The overall yield for the conversion of 5b to 5e was 55% and adequate characterization

of all compounds is summarized in Table 1 and in the Experimental Section.

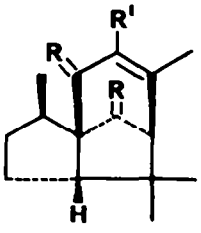
In the other route leading to 2,3,5-trimethoxytoluene (5e), a sample of 5-bromoveratraldehyde (6a) was prepared[11] by methylation of 5-bromovanillin and characterized by ^{13}C NMR (Table 1). Baeyer-Villiger oxidation[12] of the aldehyde 6a with m-chloroperbenzoic acid followed by acid hydrolisis of the resulting formate provided 5-bromo-3,4-dimethoxyphenol (6b) in 82% yield, as evidenced from the ^{1}H NMR and IR data given in the Experimental Section and the ^{13}C NMR data summarized in Table 1. Methylation of the phenol 6b with dimethylsulfate in the presence of K_2CO_3 provided 2,3,5-trimethoxybromobenzene (6c) in 93% yield. It shows ^{1}H NMR methoxyl singlets at 3.83, 3.80 and 3.76 ppm and ^{13}C NMR methoxyl signals at 55.6, 55.9 and 60.5 ppm. The preparation of 5e in this route was completed by removal of the halogen atom in 6c with MeLi followed by treatment of the organometallic intermediate with iodomethane. Compound 5e, obtained in 89% yield, was identical in all respects to 2,3,5-trimethoxytoluene (5e) obtained from 3-methylveratrole (5a).

The monocyclic sesquiterpene skeleton was constructed[9] in 79% yield by reaction of the organolithium compound derived from 5e, obtained by direct treatment with n-BuLi in dry ether, with commercially available 6-methyl-5-hepten-2-one. The reaction product 4b shows hydroxyl absorption at 3480 cm^{-1} in the IR spectrum and singlets at 76.9 ppm in the ^{13}C NMR spectrum and at 1.64 ppm (3H) in the ^{1}H NMR spectrum which are attributed to a tertiary hydroxy-bearing carbon having, in addition, a methyl group. Other significant absorption are given in the Experimental Section and in Table 1.

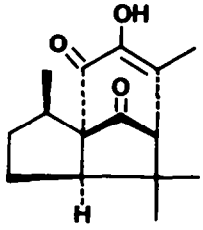
Removal of the benzylic tertiary hydroxyl group of 4b with triethylsilane[13] in the presence of BF_3, afforded (±)-leucoperezone trimethyl ether (4a) in 82% yield. It was identical in all respects, except for the optical rotation, to a sample obtained[14] by reductive methylation of (-)-perezone (1a).



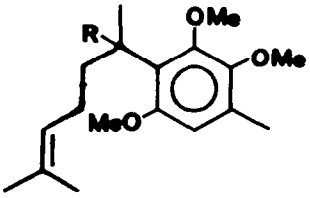
1a, R = H
b, R = Me



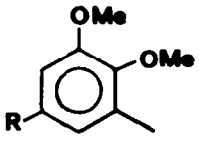
2a, R = H_2, R' = H
b, R = O, R' = OH



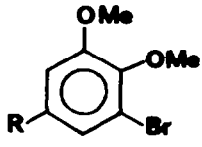
3



4a, R = H
b, R = OH



5a, R = H
b, R = NO_2
c, R = NH_2
d, R = OH
e, R = OMe



6a, R = CHO
b, R = OH
c, R = OMe

The synthesis of (±)-O-methylperezone (1b) was completed by oxidative removal of the O-methyl groups at C-1 and C-4 using silver(II)oxide[8]. Synthetic 1b was also directly compared to an authentic sample[15] of O-methylperezone (1b). Since the direct transformation of 1b to the tricyclic sesquiterpene β-pipitzol (3) has been published[1] recently, this completes a formal total synthesis of 3.

Table 1. ^{13}C NMR Chemical Shifts of the Compounds[a]

	4a	4b	5e	5d	5c	5b	5a	6c	6b	6a
C-1	154.2	152.7	155.5	154.0	142.6	143.1	123.6	156.3	154.9	132.9
C-2	126.6	125.7	97.6	99.3	98.0	105.6	110.3	99.9	101.2	110.2
C-3	151.8	151.7	152.9	154.0	152.9	152.8	152.7	153.9	155.2	151.5
C-4	145.4	146.0	141.1	141.2	139.7	152.2	147.5	140.6	140.1	153.9
C-5	128.9	130.1	131.6	132.3	132.0	132.2	131.6	117.3	117.4	117.7
C-6	108.3	109.5	105.8	109.0	108.6	118.4	122.8	107.9	110.8	128.3
C-7	15.9	15.8	15.8	16.0	15.8	16.1	15.7			
C-8	30.3	76.9								
C-9	19.6	29.9								
C-10	35.5	43.2								
C-11	27.1	23.5								
C-12	125.1	124.9								
C-13	130.6	130.5								
C-14	17.5	17.5								
C-15	25.6	25.6								
1-OMe	55.6	56.0	55.3					55.6		
3-OMe	60.5	61.2	55.6	55.9	55.5	56.1	55.5	55.9	56.2	56.2
4-OMe	59.9	59.9	60.1	60.1	60.2	60.3	59.8	60.5	60.5	60.7
CH=O										189.4

[a]Numbering of atoms is the same as for sesquiterpenic benzoquinones (see 1). The shifts are given in parts per million from internal TMS measured from $CDCl_3$ solutions, excepting 5d and 6b which were determined in Me_2CO-d_6.

EXPERIMENTAL

Melting and boiling points are uncorrected. Infrared (IR) spectra were recorded on a Perkin Elmer 421 spectrophotometer from $CHCl_3$ solutions. Ultraviolet (UV) spectra were determined by using a Unicam SP-800 spectrophotometer from 95% EtOH solutions. ^1H NMR spectra were measured with a Varian Associates EM-390 spectrometer in $CDCl_3$ solutions (unless stated otherwise) containing tetramethylsilane as the internal standard. ^{13}C NMR spectra were determined using a Varian Associates XL-100A-12-FT-16K system equiped for 5 mm O.D. sample tubes.

5-Nitro-2,3-dimethoxytoluene (5b). Neat 3-methylveratrole (5a, 1g, 6.58 mmol) was added dropwise to cooled (MeOH-ice bath) concentrated (90%) HNO_3 (14.9 g, 213 mmol) over a period of 15 min. After additional stirring at -10°C for 10 min, the reaction mixture was poured into ice-water (40 ml). The precipitate was filtered, washed with water, dried under vacuum and sublimed at 50°C/0.2 mm to yield pure 5b (1.06 g, 82%) as a yellow solid m.p. 68-69°C; IR ν_{max} 1617, 1599 (C=C) 1530 and 1351 cm^{-1} (NO_2), UV λ_{max} 2.97 (log ε 3.70) 230 nm (3.76); ^1H NMR δ 7.75 (d, J = 2.5 Hz, 1H, H-6), 7.64 (d, J = 2.5 Hz, 1H, H-4), 3.95 and 3.93 (2s, 3H each, methoxyls), 2.33 ppm (s, 3H, aromatic methyl); ^{13}C NMR, Table 1.

3,4-Dimethoxy-5-methylaniline (5c). A solution of 5b (1.05 g, 5.33 mmol) in methanol (70 ml) was hydrogenated at room temperature and atmospheric pressure (586 mm Hg), in the presence of prehydrogenated 10% palladized charcoal (100 mg) until the hydrogen uptake ceased. The catalyst was removed by filtration and the solvent evaporated. The residue gave orange crystals of 5c (845 mg, 95%) which rapidly darkens upon contact with air. They show: IR ν_{max} 3410 (NH_2) 1630, 1614 and 1505 cm^{-1} (C=C); UV λ_{max} 290 (log ε 2.98) 240 nm (3.44) 220 (3.43); ^1H NMR

δ 6.10 (br s, 2H, H-2 and H-6), 3.80 and 3.72 (2s, 3H each, methoxyls), 3.42 (br s, 2H, disappearing with D_2O, NH_2), 2.18 ppm (s, 3H, aromatic methyl); ^{13}C NMR, Table 1.

3,4-Dimethoxy-5-methylphenol (5d). A solution of 5c (0.5 g, 2.99 mmol) in 10% aq H_2SO_4 (10 ml) was treated protionwise (10 min) with $NaNO_2$ (0.4 g, 5.8 mmol) in H_2O (2 ml). The solution was then stirred at room temperature during 15 min., heated to 50°C and stirring continued for another 30 min. The cold reaction mixture was throughly extracted with EtOAc (4 x 150 ml) and the combined extracts washed (H_2O, brine), dried (Na_2SO_4) and evaporated. The oily residue (427 mg) was chromatographed over Alcoa F-20 alumina. The fractions eluted with chloroform were combined yielding 5d (351 mg, 70%) as a pale yellow viscous oil: IR ν_{max} 3610, 3350 (OH) 1622 and 1507 cm^{-1} (C=C); UV λ_{max} 282 (log ε 3.37) 226 λ nm (3.66); ^1H NMR δ 6.33 (d,J = 2.5 Hz, 1H, H-6), 6.26 (d,J = 2.5 Hz, 1H, H-2), 5.35 (br s, 1H, disappearing with D_2O, OH), 3.80 and 3.76 (2s, 3H each, methoxyls), 2.22 ppm (s, 3H, aromatic methyl); ^{13}C NMR, Table 1.

2,3,5-Trimethoxytoluene (5e). Method A: A solution of 5d (100 mg, 0.6 mmol) in dry acetone (20 ml) was treated with anhydrous potassium carbonate (165 mg, 1.2 mmol) and dimethyl sulfate (175 mg, 1.39 mmol). After refluxing for 5 h, the solvent was evaporated and the residue partitioned between Et_2O (30 ml and H_2O (15 ml). The organic layer was washed with 10% aq NaOH (3 x 10 ml), washed with H_2O (10 ml), dried (Na_2SO_4) and evaporated. The crude residue (97 mg) was percolated through a small Al_2O_3 column (5 g) using chloroform as eluent, to afford 5e (89 mg, 82%) as a viscous colorless oil: IR ν_{max} 1618 cm^{-1} (C=C); UV λ_{max} 280 (log ε 3.22) 225 nm (3.58); ^1H NMR δ 6.31 (d,J = 2.5 Hz, 1H, H-6), 6.24 (d,J = 2.5 Hz, 1H, H-4), 3.80 (s, 3H, methoxyl), 3.75 (s, 6H, two methoxyls) and 2.22 ppm (s, 3H, methyl); ^{13}C NMR, Table 1.

Method B: A solution of freshly distilled 6c (11.42 g, 46.23 mmol) in anhydrous ethyl ether (250 ml) was treated at 0°C and under nitrogen atmosphere with methyllithium (90 ml of a 1.5 M solution in ethyl ether, 135 mmol). After 15 min stirring at 0°C, iodomethane (7.317 g, 51.55 mmol) was added and stirring continued at the same temperature for another 30 min. The reaction was then quenched by the slow addition of saturated ammonium chloride solution (150 ml). The mixture was throughly extracted with EtOAc (4 x 150 ml), and the combined extracts washed (H_2O, brine), dried (Na_2SO_4), and evaporated. The oily residue (8.27 g) was distilled under reduced pressure to afford 5e (7.456 g; 89%) as a colorless oil, bp 103-105° C/1 mm, which solidifies on standing in the freezer overnight. The compound was identical to the sample obtained as indicated in method A.

5-Bromo-3,4-dimethoxyphenol (6b). m-Chloroperoxybenzoic acid (20.8 g, 0.1145 mol) was added in one portion to a solution of 5-bromoveratraldehyde[11] (11.5 g, 0.047 mol) in dry chloroform (300 ml) and the mixture refluxed under nitrogen for 45 min. After cooling, the reaction mixture was transferred to a separatory funnel, washed with saturated sodium bisulfite solution (1 x 100 ml), sodium bicarbonate solution (2 x 100 ml), and water (1 x 100 ml). Drying (Na_2SO_4) and evaporation afforded a yellow residue (10.2 g) which was taken up in methanol (150 ml), diluted with 1:1 aqueous hydrochloric acid (150 ml) and stirred at room temperature for 30 min. Partial evaporation under reduced pressure furnished a semisolid residue which was extracted into $CHCl_3$ (3 x 100 ml). The combined extracts were washed (H_2O, brine), dired (Na_2SO_4), and evaporated. The residue was recrystallized from EtOAc-hex to give pure 6b (8.949 g; 82%) as colorless prisms, mp 148-149°C. Further purification of the mother liquors afforded recovered 6a (0.583 g). The title compound shows: IR ν_{max} 3300 (OH) 1625, 1600 and 1505 cm^{-1} (C=C); UV λ_{max} 287 (log ε 3.47) 225 nm (3.80); ^1H NMR (Me_2CO-d_6) δ 8.90 (br s, 1H, OH), 6.62 (d,J = 2.5 Hz, 1H, H-6), 6.50 (d,J = 2.5 Hz, 1H, H-2), 3.85 and 3.74 ppm (2s, 3H each, methoxyls); ^{13}C NMR, Table 1.

2,3,5-Trimethoxybromobenzene (6c). A solution of 6b (10.6 g, 45.49 mmol) in dry acetone (300 ml) was treated with anhydrous potassium carbonate (12.55 g, 90.98 mmol) and dimethyl sulfate (12.7 g, 100.8 mmol). After 12 h stirring at room temperature under nitrogen, the reaction mixture was diluted with cold water (500 ml), concentrated to one-third volume, and extracted with EtOAc (3 x 100 ml). The organic extracts were washed (H_2O, brine), dried (Na_2SO_4), and evaporated. The residue (11.84 g) was purified by column chromatography on SiO_2 (300 g) using EtOAc-hex (1:9) as eluent to give 6c (10.4 g; 93%) as a colorless oil, bp 117-119° C/1 mm: IR ν_{max} 1620, 1590 and 1508 cm^{-1} (C=C); UV λ_{max} 287 (log ε 3.52) 226 nm (3.95); ^1H NMR δ 6.63 (d,J = 2.5 Hz, 1H, H-6), 6.44 (d,J = 2.5 Hz, 1H, H-4), 3.83, 3.80 and 3.76 ppm (3s, 3H each, methoxyls); ^{13}C NMR, Table 1.

(+)-8-Hydroxyleucoperezone trimethyl ether (4b). A solution of freshly distilled 5e (1.450 g, 7.967 mmol) in anhydrous ethyl ether (50 ml) was cooled to 0°C (ice--salt bath) and treated with n-butyllithium (7.5 ml of a 1.6 M solution in hexane, 12 mmol). After 30 min stirring at 0°C the formation of a white precipitate was observed and the mixture was further stirred at room temperature overnight. The resulting suspension was cooled again to 0°C and treated dropwise with neat 6-methyl-5-hepten-2-one (1.539 g, 12.21 mmol). After 30 min stirring, the cloudy reaction mixture was quenched by the addition of ammonium chloride solution (30 ml) and thoroughly extracted with EtOAc (4 x 5 ml). The combined extracts were washed (H_2O, brine), dried (Na_2SO_4), and evaporated. The yellow residue (2.31 g) was

purified by preparative thin-layer chromatography (SiO_2; 5:95 EtOAc-hex) to furnish pure 4b (1.946 g; 79%) as a thick colorless oil, and a small amount of recovered 5e (127.31 mg). The title compound shows: IR ν_{max} 3480 (OH) 1623 cm^{-1} (C=C); UV λ_{max} 285 (log ε 3.47) 223 nm (3.98); ^1H NMR δ 6.46 (s, 1H, H-6), 6.07 (s, 1H, disappears upon addition of D_2O, OH), 5.08 (t with further unresolved couplings, J_t = 7Hz, 1H, H-12), 3.90, 3.78 and 3.74 (3s, 3H each, methoxyls), 2.24 (s, 3H, aromatic methyl), 1.64 (s, 6H, one isopropylidene and one tertiary methyl) and 1.53 ppm (br s, 3H one isopropylidene methyl); ^{13}C NMR, Table 1.

(+)-Leucoperezone trimethyl ether 4a. A solution of 4b (350.2 mg, 1.137 mmol) and triethyl silane (158 mg, 1.36 mmol) in dry dichloromethane (10 ml) was cooled to -78°C and treated dropwise with boron trifluoride etherate (242.2 mg, 1.706 mmol). After 30 min stirring at -78°C, the mixture was poured into saturated $NaHCO_3$ solution (10 ml) and extracted with EtOAc (3 x 15 ml). The combined extracts were washed (H_2O, brine), dried (Na_2SO_4), and evaporated. The crude residue (291.3 mg) was percolated through a small SiO_2 column (10 g) using EtOAc-hex (3:7) as eluent, to afford 4a (272.2 mg; 82%) as a yellowish oil: IR ν_{max} 1618 cm^{-1} (C=c); UV λ_{max} 2.84 (log ε 3.16) 226 nm (3.78); ^1H NMR δ 6.37 (s, 1H, H-6), 5.09 (t with further unresolved couplings, J_t = 7 Hz, 1H, H-12), 3.81, 3.76 and 3.74 (3s, 3H each methoxyls), 2.24 (s, 3H, aromatic methyl), 1.64 and 1.53 (2 br s, 3H each, isopropylidene methyls) and 1.26 ppm (d, J = 7 Hz, 3H, secondary methyl); ^{13}C NMR, Table 1. The compound is identical by spectroscopic and chromatographic comparison to an authentic specimen[14] of leucoperezone trimethyl ether.

(+)-O-Methyl perezone (1b). A suspension of 4a (100 mg, 0.3424 mmol) and silver(II)oxide (210 mg, 1.6953 mmol) in dioxane (10 ml) was treated with 7 N nitric acid (0.4 ml) and stirred at room temperature under nitrogen for 15 min. The reaction mixture was diluted with H_2O (20 ml) and extracted with $CHCl_3$ (4 x 50 ml). The combined extracts were washed (H_2O, brine), dried (Na_2SO_4), and evaporated. The dark yellow residue (71.7 mg) was purified by preparative thin-layer chromatography (SiO_2; 3:7 EtOAc-hex) to furnish pure 1b (60.19 mg; 67%) as a yellow oil,[15] identical by spectroscopic and chromatographic comparison to an authentic sample of O-methyl perezone (1b).

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