May, 1981] © *1981 The Chemical Society of Japan* NOTES *Bull. Chem. Soc. Jpn.*, **54**, *1573—1574 (1981)* 1573

A New Route to Vitispiranes

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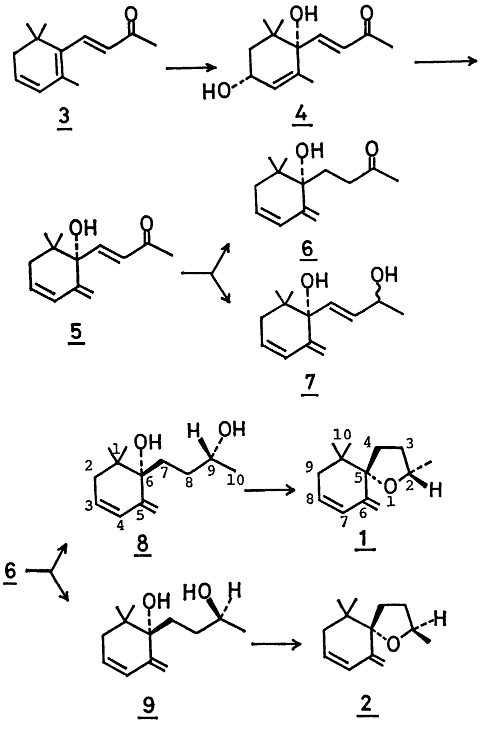
(Received April 26, 1980)

Synopsis. Diastereoisomeric vitispiranes have been synthesized from 2,6,6-trimethyl-1-(3-oxo-1-butenyl)-1,3-cyclohexadiene by five-step reactions including photooxygenation.

Vitispirane, an odoriferous C_{13} spiro-ether, was initially found in the aroma volatiles of grape juice (vine sp. *Vitis vinifera*), as well as in table and fortified wines and in distilled spirits.[1] Recently Ohloff *et al.* have also isolated vitispirane from the volatiles of a vanilla extract and have shown the presence of (2*RS*,5*RS*)- and (2*RS*,5*SR*)-vitispiranes (**1** and **2**) in the vanilla extract; their relative configurations were established by stereoselective synthesis.[2] In relation to our own interest in devising simplified approaches to the synthesis of ionone-related flavorants, we have developed an alternative synthesis of vitispiranes (**1** and **2**) from an easily accessible dehydroionone **3**.[3] Our synthetic route is outlined in the following scheme.



The photosensitized oxygenation of the dehydroionone **3**,[4] followed by the reduction of the resulting peroxide with thiourea,[5] provided the *cis*-diol **4**.[6] The subsequent treatment of **4** with dimethyl sulfoxide[7] at 140 °C for 8 h afforded the crystalline triene ketone **5** in a 47% yield. The conjugate reduction of the α,β-unsaturated ketone of **5** with $LiAlH(OMe)_3$–$CuBr$[8] in tetrahydrofuran at −20 °C provided the diene ketone **6** in a 48% yield. Although a high selectivity for 1,4-addition was reported by Semmelhack *et al.* with a variety of cyclic and acyclic α,β-unsaturated ketones,[8] the formation of a 1,2-adduct **7** in a moderate yield was also observed in the reduction of **5**. When the reagent prepared from $LiAlH_4$–CuI[9] was employed, the 1,2-adduct **7** was obtained as the major product.

The reduction of **6** with sodium borohydride in ethanol gave the diastereoisomeric diene diols, **8** and **9**, in a ratio of *ca.* 7:1. The pure **8** was obtained by the recrystallization of the mixture. The diene diol **8** was stereospecifically cyclized[10] to (2*RS*,5*RS*)-vitispirane **1** by heating with *p*-toluenesulfonyl chloride in pyridine, the relative configurations at C-6 and C-9 of **8** being established as (6*RS*,9*SR*). The filtrate fraction was chromatographed to afford a mixture containing **8** and **9** in a ratio of *ca.* 1:1. The ^1H-NMR spectrum of this mixture is practically identical with that of the pure **8** except for a pair of singlets at 5.18 and 5.20 ppm due to one of the *exo*-methylene protons of **8** and **9** respectively. The treatment of this mixture with *p*-toluenesulfonyl chloride afforded (2*RS*,5*RS*)- and (2*RS*,5*SR*)-vitispiranes (**1** and **2**) in a ratio of *ca* 1:1.

Experimental

The melting points are uncorrected. The following spectrometers were used: IR, Hitachi 215; NMR, Varian XL-100 or JOEL FX-100 (tetramethylsilane as the internal standard); mass spectra, JEOL D-300. The thin-layer chromatography (TLC) was performed on 0.25 mm precoated silica gel PF_{254} (Merck). Silica gel (70—230 mesh, Merck) was used for the column chromatography.

cis-2,6,6-Trimethyl-1-(3-oxo-1-butenyl)-2-cyclohexene-1,4-diol (4). A solution of dehydroionone **3** (3.00 g, 15.8 mmol, purity 85%) and Rose Bengal (30 mg) in methanol (50 ml) was irradiated externally with a high-pressure mercury vapor lamp (Toshiba HT-400PL) in a water-cooled (0—5 °C) apparatus, while oxygen was being bubbled through the solution (*ca.* 30 ml/min). The reaction was essentially complete after 25 min. After the addition of thiourea (1.37 g, 18.0 mmol), the mixture was stirred at 25 °C for 7 h. After the subsequent removal of the solvent, the residue was chromatographed (benzene–ethyl acetate, 1:1) on silica gel to give the *cis*-diol **4** (0.80 g, 28%). **4**: IR (neat) 3400, 1672, 1620, 1098, 1015, 988 cm^{-1}; NMR ($CDCl_3$) δ 0.97 (s, 3H), 0.99 (s, 3H), 1.65 (t, $J=2$ Hz, 3H), 1.60—2.16 (m, 4H), 2.88 (s, 3H), 4.25 (m, 1H), 5.65 (m, 1H), 6.43 (d, $J=16$ Hz, 1H), 6.74 (d, $J=16$ Hz, 1H): MS, *m/e* 224 (M^+), 191, 150, 108, 43. Found: *m/e* 224.1418. Calcd for $C_{13}H_{20}O_3$: M, 224.1412.

6,6-Dimethyl-2-methylene-1-(3-oxo-1-butenyl)-3-cyclohexen-1-ol (5). A solution of the *cis*-diol **4** (1.50 g, 6.70 mmol) in dimethyl sulfoxide (6.5 g) was heated at 140 °C for 8 h. The reaction mixture was then cooled, poured into water, and extracted with ethyl acetate. The ethyl acetate extracts were washed with water and dried over anhydrous sodium sulfate. After the removal of the solvent, the residue was chromatographed (benzene– ethyl acetate, 7:1) on silica gel to give the triene ketone **5** (0.65 g, 47%). **5**: mp 81—82 °C; IR (Nujol) 3490, 1785, 1682, 1655, 1595, 1140, 995, 978, 892 cm^{-1}; NMR ($CDCl_3$) δ 0.92 (s, 3H), 0.96 (s, 3H), 1.69 (s, 1H), 2.06—2.20 (m, 2H), 2.25 (s, 3H), 5.02 (s, 1H), 5.16 (s, 1H), 5.62—5.86 (m, 1H), 6.08—6.26

(m, 1H), 6.43 (d, J=16 Hz, 1H), 6.89 (d, J=16 Hz, 1H); MS, *m/e* 206 (M$^+$), 191, 163, 121, 43. Found: *m/e* 206.1270. Calcd for $C_{13}H_{18}O_2$: M, 206.1305.

*6,6-Dimethyl-2-methylene-1-(3-oxobutyl)-3-cyclohexen-1-ol (**6**).* A solution of lithium trimethoxyaluminium hydride in tetrahydrofuran (0.659 mol/l, 60.7 ml, 40.0 mmol) was added, drop by drop, to a suspension of copper(I) bromide (2.86 g, 20.0 mmol) in tetrahydrofuran (15 ml) at −20 to −10 °C. After 30 min, the resulting dark brown suspension was cooled to −20 °C. A solution of the triene ketone **5** (1.03 g, 5.00 mmol) in tetrahydrofuran (10 ml) was added (*ca.* 5 min). The mixture was then stirred at −20 °C for 50 min, poured into cold water, and extracted with ethyl acetate. The ethyl acetate extracts were washed with water and dried over anhydrous sodium sulfate. After the removal of the solvent, the residue was chromatographed (hexane–ethyl acetate, 5:4) on silica gel to give the diene ketone **6** (490 mg, 48%) and the triene diol **7** (499 mg, 49%). **6**: mp 60—62 °C; IR (Nujol) 3320, 3025, 1782, 1715 (weak), 1642, 1600, 1106, 1042, 892 cm^{-1}; NMR ($CDCl_3$) δ 0.8—1.2 (m, 6H, with two s at 0.88 and 1.06), 1.4—2.6 (m, 10H, with a d at 1.62 and a s at 2.14), 4.80—5.16 (m, 2H), 5.32—5.68 (m, 1H), 5.90—6.12 (m, 1H); MS *m/e* 208 (M$^+$), 190, 185, 150, 131, 99, 43. Found: *m/e* 208.1458. Calcd for $C_{13}H_{20}O_2$: M, 208.1461.

*1-(3-Hydroxybutyl)-6,6-dimethyl-2-methylene-3-cyclohexen-1-ols (**8** and **9**).* A solution of the diene ketone **6** (439 mg, 2.11 mmol) and sodium borohydride (300 mg, 7.93 mmol) in ethanol (15 ml) was stirred at 25 °C for 1 h. The reaction mixture was then poured into water and extracted with ethyl acetate. The ethyl acetate extracts were washed with water and dried over anhydrous sodium sulfate. After the removal of the solvent, the crystalline residue was recrystallized from hexane–ethyl acetate to yield **8** (179 mg). The filtrate was concentrated and crystallized again from hexane–ethyl acetate to yield **8** (90 mg). The filtrate was concentrated and chromatographed (hexane–ethyl acetate, 2:5) on silica gel to give a mixture containing **8** and **9** in a ratio *ca.* 1:1 (91 mg). The total yield of **8** and **9** was 81%. **8**: mp 141—142 °C; IR (Nujol) 3300, 3020, 1780, 1640, 1598, 1048, 988, 890 cm^{-1}; NMR ($CDCl_3$) δ 0.88 (s, 3H), 1.06 (s, 3H), 1.16 (d, J=6 Hz, 3H), 1.26—2.46 (m, 8H), 3.56—3.92 (m, 1H), 5.04 (s, 1H), 5.02 (s, 1H), 5.50—5.72 (m, 1H), 6.00—6.18 (m, 1H); MS, *m/e* 210 (M$^+$), 192 177, 126, 43. Found: *m/e* 210.1672. Calcd for $C_{13}H_{22}O_2$: M, 210.1620.

*Vitispiranes (**1** and **2**).* To a solution of the diene diol **8** (1.007 g, 4.79 mmol) in pyridine (13 ml), was added *p*-toluenesulfonyl chloride (1.57 g, 8.24 mmol). The mixture was then stirred at 0 °C for 18 h, heated at 80 °C for 4 h, and cooled to 0 °C. After the addition of water (6 ml), the mixture was stirred at 0 °C for 1 h, poured into water, and extracted with ether–pentane. The organic layers were washed with water and dried over anhydrous sodium sulfate. After the removal of the solvent, the residue was distilled (oil bath 100 °C/1 Torr) to give (2*RS*,5*RS*)-vitispirane **1** (812 mg, 88%). The mixture of **8** and **9** from the previous experiment, upon treatment under the same conditions, afforded (2*RS*,5*RS*)- and (2*RS*,5*SR*)-vitispiranes (**1** and **2**) in a ratio of *ca.* 1:1. The IR, NMR, and mass spectral data of **1** and **2** were identical with those of authentic samples.[2]

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