Total Synthesis of (−)-Vitrenal and Its Biological Activity

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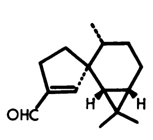
(−)-Vitrenal, the enantiomer of the natural sesquiterpene aldehyde isolated from a liverwort, has been synthesized starting from (+)-3-carene, and its activity as a plant-growth regulator has been tested.

(+)-Vitrenal ((+)-**1**) is a tricyclic sesquiterpene aldehyde isolated by Matsuo et al. from a liverwort, *Lepidozia vitrea*, together with its possible biogenetic precursor, isobicyclogermacrenal (**2**), and lepidozenal (**3**).[1] All of these compounds have been shown to possess potent plant-growth inhibitory activity.[1] Because of its unique carbon skeleton as well as the biological activity, we have attempted a total synthesis of (−)-vitrenal ((−)-**1**), the enantiomer of the natural product, from easily accessible (+)-3-carene. Successful synthesis of (−)-**1** would provide us with a rare chance to test the growth-regulating activity of unnatural enantiomer. Although a synthesis of (±)-vitrenal has been reported by Magari et al.,[2] and our approach is somewhat similar to theirs, we describe our synthesis herein because we have successfully achieved stereocontroled C–C bond formation in two crucial steps by employing Claisen rearrangement. We also describe the result of our biological test.



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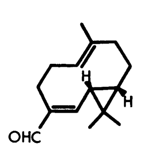

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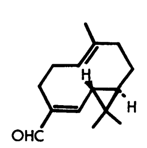

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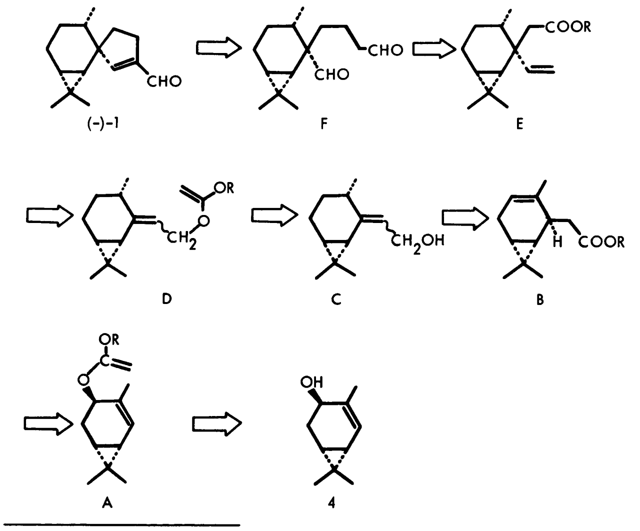
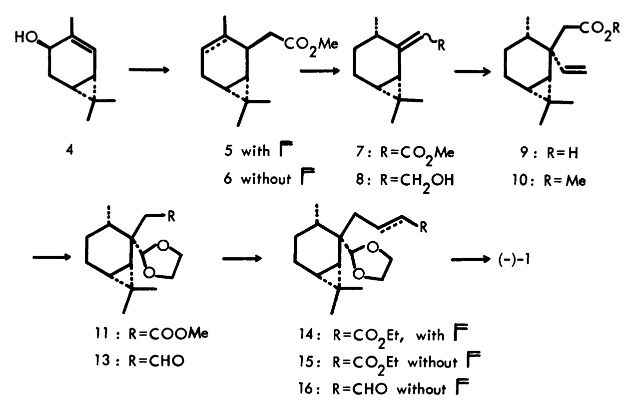
Results and Discussion

Our synthetic strategy is shown in the form of retrosynthesis. The first Claisen rearrangement (A→B) would proceed in high stereoselectivity. The reduction of double bond in B would proceed from *β*-face due to the presence of a bulky dimethylcyclopropyl ring. Introduction of double bond, the formation of C, may not be selective, but both geometrical isomers would afford the same carboxylic ester E after the 2nd Claisen rearrangement, as long as the vinyl terminus approaches the allyl part from the less hindered and therefore favored *β*-face. Elongation of ester chain and cleavage of double bond in E to the dialdehyde F, and its aldol condensation should be unambiguous.



Starting with 2-caren-4*β*-ol (**4**), obtained by the known procedure,[3] the first Claisen rearrangement was performed: Heating **4** at 137° with excess triethyl orthoacetate in the presence of propionic acid induced vinyl ether formation and its Claisen rearrangement in one pot to afford, after hydrolysis and methylation, the methyl ester **5** in 65% yield. Catalytic hydrogenation (Pd–C) of **5** afforded the saturated ester **6** in quantitative yield. However, gas chromatographic analysis of **6** revealed the presence of stereoisomers in the ratio of 95:5. Assignment of the stereochemistry for the major isomer rests on the consideration of steric requirement in hydrogenation described above. Since the separation of the isomers was possible only by gas chromatography, the mixture was used in the following steps.

Phenylselenylation followed by oxydative deselenylation of **6** gave the unsaturated ester **7** in 75% yield. As was expected (vide supra), **7** was a 1:1 mixture of geometrical isomers. Although the isomers were separated by gas chromatography and properly characterized, the mixture was used without separation for further steps. The ester **7** was reduced with diisobutylaluminum hydride (DIBAL) to give the allylic alcohol **8** in 91% yield. The geometrical isomers were



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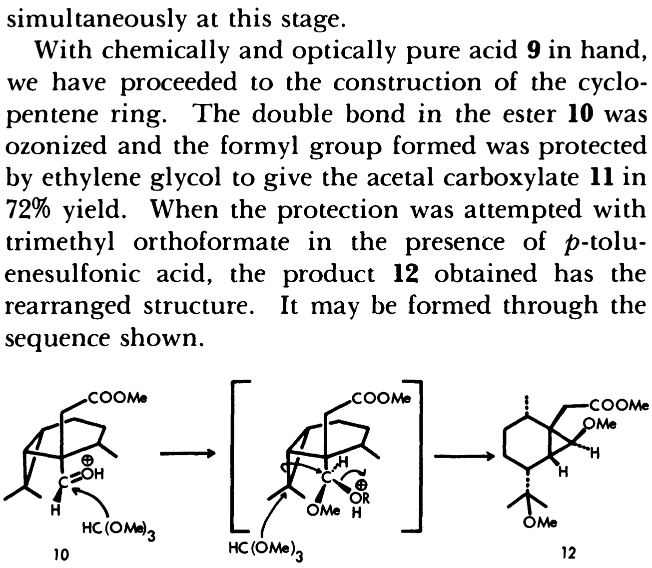
possible to separate only by gas chromatography.

For the introduction of the second carbon chain, Claisen rearrangement was again applied on the mixture **8**. Heating **8** with excess triethyl orthoacetate under the conditions similar to the previous reaction, and the subsequent alkaline hydrolysis furnished a single crystalline acid **9** in 56% yield. Its methyl ester **10** gives a single peak on GLC, while the methyl ester of the acidic mother liquor exhibited the same major peak along with a minor peak. Thus both geometrical isomers must have yielded the same acid **9** as expected.[4] We have thus removed the undesired stereoisomer on the secondary methyl group simultaneously at this stage.

With chemically and optically pure acid **9** in hand, we have proceeded to the construction of the cyclopentene ring. The double bond in the ester **10** was ozonized and the formyl group formed was protected by ethylene glycol to give the acetal carboxylate **11** in 72% yield. When the protection was attempted with trimethyl orthoformate in the presence of *p*-toluenesulfonic acid, the product **12** obtained has the rearranged structure. It may be formed through the sequence shown.



DIBAL reduction of **11** and pyridinium chlorochromate (PCC) oxidation of the resulted alcohol gave the acetal aldehyde **13** in 90% yield. Wittig reaction of **13** with (ethoxycarbonylmethylene)triphenylphosphorane went smoothly and the unsaturated ester **14** was obtained in 95% yeild. Catalytic reduction of **14** (to **15**) and subsequent DIBAL reduction followed by PCC oxidation afforded the acetal aldehyde **16**. Finally, treatment of **16** with hydrochloric acid accomplished deacetalization and aldol condensation in one pot to afford (−)-**1**. IR and NMR spectra of the product were identical and the specific rotation ($[\alpha]_D^{18}$ −113°) is completely opposite with those of natural vitrenal ($[\alpha]_D$ +107°).[1]

Although the biological activities of enantiomers have extensively been investigated in the field of insect pheromones,[5] the similar studies on growth regulators are rather scarce probably because natural regulators usually have rather complicated structures and synthesis of the unnatural enantiomer is not easy. The present synthesis of (−)-**1** gave us a good opportunity to compare the activity of the enantiomeric pair. Thus, we have carried out biological test using rice seedling and lettuce hypocotyl. While natural (+)-**1** shows a strong inhibition (I_{50}=18 ppm),[1] (−)-**1** exhibited a weak promotion (P_{50}=2.18×10^3 ppm) in the former test and a weak inhibition (I_{50}=27.79×10^3 ppm) for the latter. To the best of our knowledge, this is the first enantiomeric pair tested for the growth-regulating activity in higher plants.

Experimental

General. Melting points reported herein were taken with a YANACO melting point apparatus and are uncorrected. The ^{1}H NMR spectra were obtained on a Varian EM-390, a Varian XL-200 and/or a JEOL FX 90Q spectrometer. Chemical shifts are reported in ppm downfield from internal tetramethylsilane. Infrared spectra were recorded on a JASCO IR-2 diffraction grating infrared spectrometer. Mass spectra were measured on a HITACHI M-52 mass spectrometer and high resolution mass spectra on a JEOL JMS-01S02 mass spectrometer. Elemental analyses were performed on a YANAGIMOTO-CHN Coder. Gas chromatogram were recorded on a Shimadzu GC-6A. Optical rotation was measured on a UNION Automatic Digital Polarimeter, PM101.

(+)-Methyl 2β-(3-Caren-2-yl)acetate (5). A mixture of 2-caren-4-ol[3] (**4**, 10.6 g), propionic acid (0.6 ml) and triethyl orthoacetate (129 ml, 6.0 equiv) was heated at 136—137 °C for 20 h, and the reaction mixture was hydrolyzed with KOH (25.76 g) in 50% aq methanol (600 ml) under reflux for 4 h. After cooling, the reaction mixture was diluted with water and washed with ether. Separated aqueous layer was neutralized with 2 M HCl (1 M=1 mol dm^{-3}), and then extracted with ether. After washed with water and brine and dried over anhydrous $MgSO_4$, the ether extract was treated with diazomethane at room temperature for 30 min, and the solvent was distilled off. The residue was chromatographed on SiO_2 column (hexane:ether=10:1) to give 9.437 g (65% yeild) of **5**. Bulb-to-bulb distillation at 75 °C, 0.05 mmHg (1 mmHg=133.322 Pa), furnished the analytical sample as a colorless oil: IR (neat) 1734 cm^{-1}; ^{1}H NMR (CCl_4) δ=0.88, 1.03 (2s, 6H, $2CH_3$), 1.63 (s, 3H, CH_3), 3.63 (s, 3H, $COOCH_3$), 5.21 (s, b, 1H, C=CH); MS *m/z* 208 (M^+); $[\alpha]_D^{24}$+6.5° (*c* 1.75, MeOH). Found: C, 75.25; H, 9.70. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68.

(−)-Methyl 2β-(2-Caranyl)acetate (6). **5** (3.00 g) was hydrogenated (3 Atm) in methanol (75 ml) at room temperature over palladium charcoal (600 mg) for 3 h. Filtration of the catalyst and evaporation of the solvent gave 3.027 g (100% yield) of **6**, colorless liquid. Gas chromatography of **6** disclosed the presence of two isomers in the ratio of 95:5 (DEG-S 15%, 130 °C). Preparative gas chromatography furnished the analytical sample of **6**, colorless oil: IR (neat) 1734 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.93 (d, 3H, *J*=10.5 Hz, CH_3), 0.96 (s, 6H, $2CH_3$), 3.66 (s, 3H, $COOCH_3$); MS *m/z* 210 (M^+); $[\alpha]_D^{24}$ −150° (*c* 1.28, MeOH). Found: C, 73.96; H, 10.56. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54.

Methyl 2-Caranylideneacetate (7). To a solution of lithium diisopropylamide (22.8 mmol) in dry tetrahydrofuran (50 ml) was added **6** (11.4 mmol) dropwise at −78 °C under argon atmosphere. After stirring for 30 min, benzeneselenenyl chloride (4.336 g) in dry tetrahydrofuran (5 ml) was added dropwise rapidly, and stirring was continued overnight at room temperature. Addition of water, extraction with ether, drying over anhydrous $MgSO_4$ and evaporation of the solvent gave, after short SiO_2 column chromatography (hexane:ether=10:1), 3.281 g (76% yield) of phenylseleno compound.

To the phenylseleno compound in methanol (50 ml) was added $NaIO_4$ (4.438 g) in water (50 ml) with vigorous stirring. After 2 h, the product was extracted with ether. The extract was washed with water, saturated $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent and SiO_2 chromatography of the residue (hexane:ether=50:1) gave 1.790 g (75%) of **7** as a colorless oil. Gas chromatographic analysis showed two peaks in the ratio of nearly 1:1 (DEG-S 15%, 160 °C). Each peak was separated by preparative gas chromatography to give analytical specimens. **7a**: IR (neat) 1710, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.82, 1.04 (2s, 6H, $2CH_3$), 1.19 (d, 3H, J=7.2 Hz, CH_3), 3.71 (s, 3H, $COOCH_3$), 5.82 (t, 1H, J=1.8 Hz, C=CH); MS m/z 208 (M^+). **7b**: IR (neat) 1704, 1604 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.95 (s, 3H, CH_3), 1.09 (d, 3H, J=7.2 Hz, CH_3), 1.10 (s, 3H, CH_3), 3.67 (s, 3H, $COOCH_3$), 5.84 (s, 1H, C=CH); MS m/z 208 (M^+).

2-(2-Caranylidene)ethanol (8). A mixture of **7a** and **7b** (800 mg) in dry hexane (20 ml) was stirred at 0 °C for 2 h with 1 M DIBAL solution (11 ml) under argon atmosphere. After saturated NH_4Cl (10 ml) was added, organic layer was separated and aqueous layer was extracted with ether. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 and then solvent was evaporated. The residue was chromatographed on SiO_2 (hexane:ether=1:1) to give 700 mg (91%) of **8** with two components as a colorless oil. Preparative gas chromatography (DEG-S 15%, 160 °C) separated each component **8a**: IR (neat) 3317, 1634 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.85 (s, 3H, CH_3), 1.02 (d, 3H, J=7.2 Hz, CH_3), 1.09 (s, 3H, CH_3), 4.24 (t, 2H, J=7.2 Hz, $=HCCH_2O$), 5.58 (t, 1H, J=7.2 Hz, C=CH); MS m/z 180 (M^+). **8b**: IR (neat) 3300, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.89 (s, 3H, CH_3), 0.95 (d, 3H, J=7.2 Hz, CH_3), 1.05 (s, 3H, CH_3), 4.23 (m, 2H, $=CH-CH_2O$), 5.58 (t, 1H, J=7.2 Hz, C=CH); MS m/z 180 (M^+).

(−)-(2-Vinyl-2-caranyl)acetic Acid (9). A mixture of **8** (500 mg) and triethyl orthoacetate (6.3 ml) was heated in benzene (30 ml) at 140 °C for 10 h in the presence of a trace of propionic acid. After evaporation of the excess triethyl orthoacetate, the reaction mixture was heated under reflux overnight with KOH (454 mg) in 50% aq methanol (50 ml). The reaction mixture was diluted with water and washed throughly with ether to remove neutral materials. The aqueous solution was neutralized with 2 M HCl, and then extracted with ether. The $MgSO_4$-dried ether extract gave, after evaporation of the solvent, 350 mg (56% yield) of crystals. Recrystallization in 20% aq methanol gave 311 mg of **9**, colorless needles, mp 85—87 °C: IR (KBr) 1693, 1634 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.83 (d, 3H, J=6.5 Hz, CH_3), 0.99, 1.08 (2s, 6H, $2CH_3$), 2.62 (s, 2H, CH_2CO_2), 4.9—5.1 (m, 2H, $C=CH_2$), 5.96 (dd, 1H, J=17.5, 10.5 Hz, C=CH); MS m/z 222 (M^+); $[\alpha]^{24}_{\mathrm{D}}$ −145° (c 1.12, MeOH). Found: C, 75.62; H, 10.06. Calcd for $C_{14}H_{20}O_2$: C, 75.63; H, 9.97.

(−)-Methyl(2-vinyl-2-caranyl)acetate (10). Treatment of **9** (250 mg) with diazomethane furnished, after SiO_2 chromatography (hexane:ether=10:1), the methyl ester **10** (267 mg, 100%) as a colorless oil. IR (neat) 1736, 1676 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.82 (d, 3H, J=7.5 Hz, CH_3), 1.02, 1.10 (2s, 6H, $2CH_3$), 2.58 (s, 2H, CH_2CO_2), 3.63 (s, 3H, OCH_3), 4.9—5.1 (m, 2H, $C=CH_2$), 5.94 (dd, 1H, J=17.5, 10.5 Hz, CH=C); $[\alpha]^{24}_{\mathrm{D}}$ −125° (c 1.12, MeOH). Found: m/z 236.1787. Calcd for $C_{15}H_{24}O_2$: M, 236.1775.

Acetal Carboxylate 11. Ozone was passed through a solution of **10** (200 mg) in methanol (10 ml) at −78 °C for 1 h and reductive (Me_2S) work up of the reaction mixture gave an oily aldehyde (180 mg) which was converted without purification to **11** by heating it with ethylene glycol in dry benzene in the presence of catalytic amount of p-toluenesulfonic acid. Chromatographic separation on SiO_2 column (hexane:ether=10:1) afforded 173 mg (72% yield) of **11** as a colorless oil: IR (CCl_4) 1726 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.93 (d, 3H, J=7.5 Hz, CH_3), 1.00, 1.15 (2s, 6H, $2CH_3$), 2.49 (d, 1H, J=13.5 Hz, CH_2CO_2), 2.70 (d, 1H, J=13.5 Hz, CH_2CO_2), 3.63 (s, 3H, OCH_3), 3.6—4.0 (m, 4H, $O(CH_2)_2O$), 4.78 (s, 1H, $\mathrm{HC}{<}^{\mathrm{O}}_{\mathrm{O}}$); $[\alpha]^{24}_{\mathrm{D}}$ −135° (c 1.12, MeOH). Found: m/z 282.1847. Calcd for $C_{16}H_{26}O_4$: M, 282.1830.

Compound 12. Methyl ester **10** (40 mg), OsO_4 (2 mg), and $NaIO_4$ (90 mg) were stirred overnight in 50% aq tetrahydrofuran. After dilution, the reaction mixture was extracted with ether. Normal work-up and evaporation yielded an oily aldehyde (40 mg). Without purification, the aldehyde was stirred overnight with trimethyl orthoformate (291 mg), and p-toluenesulfonic acid (catalytic amount). Neutralization, extraction with ether, drying, evaporation and finally SiO_2 chromatography afforded 31 mg (68%) of **12**, a colorless liquid. IR (neat) 1726 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.91 (d, 3H, J=7.0 Hz, CH_3), 1.18, 1.22 (2s, 6H, $2CH_3$), 2.25 (d, 1H, J=16.3 Hz, CH_2CO_2), 2.62 (d, 1H, J=16.3 Hz, CH_2CO_2), 3.04 (d, 1H, J=3.2 Hz, CHO), 3.19, 3.31 (2s, 6H, $2OCH_3$), 3.68 (s, 3H, CO_2Me); MS m/z 284 (M^+).

Acetal Aldehyde 13. Compound **11** (130 mg) was reduced with DIBAL in hexane at −78 °C for 30 min. The reaction was quenched with water (1 ml) and the product was extract with ether. Evaporation of the solvent gave 123 mg of the mixture of **13** and the corresponding alcohol.

Without purification, the mixture (123 mg) was oxidized with pyridinium chlorochromate (278 mg) in dichloromethane (10 ml). After stirring for 1 h, ether (10 ml) was added and stirred for 5 min and then filtrated. Evaporation of the solvent, and SiO_2 chromatography (hexane:ether=1:1) of the residue gave 102 mg (90%) of **13**, a colorless oil: IR (CCl_4) 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.96 (d, 3H, J=7.5 Hz, CH_3), 1.02, 1.17 (2s, 6H, $2CH_3$), 2.34 (dd, 1H, J=15.0; 3.6 Hz, CH_2CO), 2.76 (dd, 1H, J=15.0; 3.6 Hz, CH_2CO), 3.7—3.9 (m, 4H, $O(CH_2)_2O$), 4.78 (s, 1H, $\mathrm{HC}{<}^{\mathrm{O}}_{\mathrm{O}}$), 9.89 (t, 1H, J=3.6 Hz, CHO); $[\alpha]^{24}_{\mathrm{D}}$ −122.5° (c 1.12, MeOH). Found: m/z 208.1456 ($-C_2H_4O$). Calcd for $C_{15}H_{24}O_3$: M, 252.1724.

Wittig Reaction of 13 (synthesis of 14). Benzene (10 ml) solution of **13** (100 mg) and (ethoxycarbonylmethylene)triphenylphosphorane (331 mg) was heated under reflux for 12 h. The solvent was removed in vacuo, and the residue was chromatographed on SiO_2 column (CH_2Cl_2) to give **14** (116 mg, 95%) as a colorless oil: IR (CCl_4) 1713, 1642 cm^{-1}; ^1H NMR (CCl_4) δ=0.88 (d, 3H, J=6.6 Hz, CH_3), 1.01, 1.14 (2s, 6H, $2CH_3$), 1.28 (t, 3H, J=6.6 Hz, OCH_2CH_3), 2.45 (d, 2H, J=9.0 Hz, CH_2), 3.8—4.0 (m, 4H, $O(CH_2)_2O$), 4.11 (q, 2H, J=6.6 Hz, OCH_2CH_3), 4.73 (s, 1H, $\mathrm{HC}{<}^{\mathrm{O}}_{\mathrm{O}}$), 5.73 (d, 1H, J=15.6 Hz, $CH=CHCO_2Et$), 6.91 (dd, 1H, J=15.6; 6.6 Hz, $CH= CH-CO_2Et$); $[\alpha]^{24}_{\mathrm{D}}$ −83° (c 1.12, MeOH). Found: m/z 322.2142. Calcd for $C_{19}H_{30}O_4$: M, 322.2142.

Acetal Butanoate 15. Catalytic reduction of **14** (50 mg) in methanol (3 ml) over palladium charcoal (5 mg) furnished, after filtration of the catalyst and evaporation of the solvent, **15**, a colorless oil, in quantitative yield. IR (CCl_4) 1712 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.89 (d, 3H, J=7.2 Hz, CH_3), 0.99, 1.15 (2s, 6H, $2CH_3$), 1.26 (t, 3H, J=7.2 Hz, OCH_2CH_3), 3.4—3.9 (m, 4H, $O(CH_2)_2O$), 4.13 (q, 2H, J=7.2 Hz, OCH_2CH_3) and 4.75 (s, 1H, $HC\overset{O}{\underset{O}{<}}$); $[\alpha]_D^{24}$ −75° (*c* 1.12, MeOH). Found: *m/z* 324.2257. Calcd for $C_{19}H_{32}O_4$: M, 324.2299.

Acetal Aldehyde 16. Compound **15** (36 mg) was reduced with 1.2 equivalent of DIBAL at −78 °C in dry hexane (2 ml) under argon atmosphere. After stirring for 30 min, the reaction was quenched with water. Extraction with ether furnished a mixture (30.2 mg) of **16** and the corresponding alcohol.

The mixture was oxidized in CH_2Cl_2 (1 ml) with pyridinium chlorochromate (78 mg). After stirring for 1 h, ether (5 ml) was added and the reaction mixture was filtrated. Evaporation of the solvent and SiO_2 chromatography (hexane: ether=1:1) gave 28.6 mg (85%) of **16** as a colorless oil. IR (CCl_4) 1716, 1453 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.89 (d, 3H, J=7.2 Hz, CH_3), 0.99, 1.15 (2s, 6H, $2CH_3$), 3.66—3.99 (m, 4H, $O(CH_2)_2O$), 4.74 (s, 1H, $HC\overset{O}{\underset{O}{<}}$), 9.77 (t, 1H, J=2.3 Hz, CHO); $[\alpha]_D^{20}$ −102.5° (*c* 0.5, MeOH). Found: *m/z* 280.2037. Calcd for $C_{17}H_{28}O_3$: M, 280.2037.

(−)-Vitrenal ((−)-1). Compound **16** (20 mg) in THF (2.4 ml) was heated for 6 h under reflux with 10% of aq HCl (0.6 ml). The reaction mixture was diluted with water, neutralized by saturated aq $NaHCO_3$, and extracted with ether. Evaporation of the solvent and short column SiO_2 chromatography afforded 14.7 mg (94%) of (−)-**1**. IR (CCl_4) 1680, 1614, 854 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.77 (d, 3H, J= 5.5 Hz, CH_3), 0.94, 1.17 (2s, 6H, $2CH_3$), 6.86 (t, 1H, J=1.5 Hz, CH=C), 9.76 (s, 1H, CHO); $[\alpha]_D^{18}$ −113° (*c* 0.4, MeOH). Found: *m/z* 218.1673. Calcd for $C_{15}H_{22}O$: M, 218.1670.

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