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SYNTHESIS OF (±)-VITRENAL

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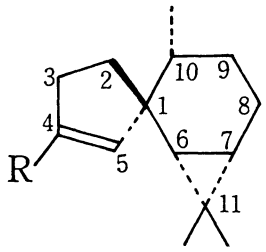
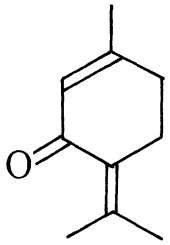
(±)-Vitrenal (**1**), a sesquiterpene aldehyde with a novel vitrane skeleton, was synthesized from a monoterpene piperitenone (**2**) by 12-step reactions in *ca.* 7% overall yield. 2-Formyl-isocarane, derived from **2** *via* (±)-isocaran-2-one was allylated stereospecifically and, after protection of the formyl group, the allyl chain was modified to a 4-methoxy-3-butenyl group. Acid treatment of the masked dialdehydic intermediate yielded **1** by concomitant deprotection and aldol condensation.

(+)-Vitrenal is a plant-growth inhibitory sesquiterpene isolated from the liverwort *Lepidozia vitrea* STEPH., its structure (**1**) including absolute configuration being determined unambiguously by X-ray diffraction analysis.[1] This communication deals with a synthesis of (±)-vitrenal with a novel vitrane[1] skeleton, the tetramethylated spiro[4.5]decane system fused with a cyclopropane ring.

The starting monoterpene, piperitenone (**2**) was converted in 4 steps into isocaran-2-one (**5**),[2,3] *via* car-2-ene (**3**)[2,4] and *cis*-caran-*trans*-2-ol (**4**)[2,5] by the known procedures. Treatment of diphenyl(methoxymethyl)phosphine oxide with LDA in THF gave its lithium derivative,[6] which was treated with **5** to give a mixture (*ca.* 1:3) of geometrical isomers of methoxymethylene derivatives (**6a** and **6b**) in *ca.* 30% yield.[7] Acid hydrolysis (aq. HCl in THF, reflux) of the mixture (**6**) gave an aldehyde (**7**)[8] in 97% yield. A stereoselective introduction of a



1 R = CHO
13 R = CH_2OH



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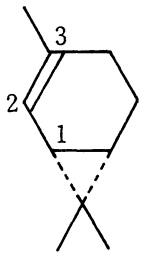
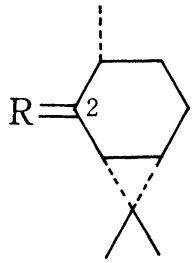
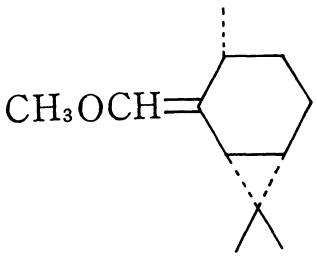


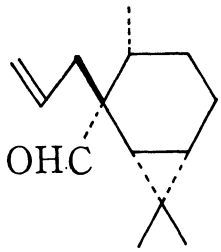
3



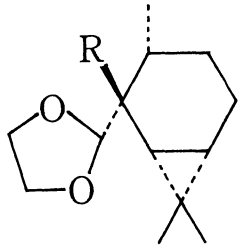
4 R = α-H, β-OH
5 R = O
7 R = CHO, H



6



8



9 R = $CH_2CH{=}CH_2$
10 R = $CH_2CH_2CH_2OH$
11 R = CH_2CH_2CHO
12 R = $CH_2CH_2CH{=}CHOCH_3$

2-propenyl group was carried out by treatment of the aldehyde (**7**) with KH in THF[9] and then with 2-propenyl bromide to give **8** as a sole product in *ca.* 90% yield. The 2-propenyl group of **8** would be in a β disposition as a result of an attack of the reagent to the C-2 position from the less hindered β-side of intermediate enolate anion derived from **7**. This stereochemical assignment was confirmed by the transformation of **8** into (±)-**1** as shown below.

After the aldehyde group of **8** was protected as an ethylene acetal (**9**, obtained in 80% yield), **9** was subjected to hydroboration with diborane in THF followed by treatment with alkaline hydrogen peroxide to give an alcohol (**10**) in almost quantitative yield. An aldehyde (**11**) was obtained quantitatively by oxidation of **10** with CrO_3-pyridine complex in CH_2Cl_2. Finally, treatment of **11** with the lithium derivative of diphenyl(methoxymethyl)phosphine oxide[6] in THF gave a methoxymethylene derivative (**12**)[10] in *ca.* 60% yield, which was hydrolyzed (aq. HCl in THF, reflux) to afford (±)-vitrenal in 71% yield.[11]

The ^1H NMR, UV, and mass spectra of the synthetic (±)-vitrenal were found to

be identical with those of natural (+)-vitrenal (**1**).[1] Reduction of (±)-vitrenal with $LiAlH_4$ gave the corresponding alcohol whose ^1H and ^{13}C NMR and mass spectral data are identical with those of the alcohol (**13**)[1] derived from (+)-vitrenal. Thus, (±)-vitrenal was synthesized from piperitenone (**2**) in an overall yield of *ca.* 7%.

Characterization of **1**, **6**-**12**, and **13** is as follows; (±)-**1**: oil, IR (neat) 2800, 2710, 1680, and 1615 cm^{-1}; UV (EtOH) λ_{max} 242 nm(ε 10,400); ^1H NMR ($CDCl_3$)[12] δ 0.7-0.8 (2H, m), 0.78 (3H, d, J = *ca.* 5 Hz), 0.96 (3H, s), 1.19 (3H, s), 6.85 (1H, t, J = 1.5 Hz), and 9.77 (1H, s); $C_{15}H_{22}O$ [*m/z* 218.1667($M^{+\cdot}$)];[13] **6**: each component of the geometrical isomers (**6a** and **6b**) was separated by column chromatography (SiO_2); **6a**(less polar on TLC): oil, ^1H NMR δ 0.85 (3H, s), 0.90 (3H, d, J = 7 Hz), 1.00 (3H, s), 3.54 (3H, s), and 5.80 (1H, br. s); **6b**(more polar on TLC): oil, ^1H NMR δ 0.84 (3H, s), 0.94 (3H, d, J = 6 Hz), 1.06 (3H, s), 3.51 (3H, s), and 5.80 (1H, br. s); **7**: oil, IR (neat) 1730 cm^{-1}; ^1H NMR δ 0.5-0.75 (2H, m), 0.90 (3H, d, J = 6 Hz), 1.01 (3H, s), 1.06 (3H, s), and 9.63 (1H, d, J = 2 Hz); **8**: oil, IR (neat) 1725, 1640, and 920 cm^{-1}; ^1H NMR δ 0.5-0.75 (2H, m), *ca.* 0.88 (3H, diffused d), 1.04 (6H, s), 5.0-6.1 (3H, m), and 9.50 (1H, br. s); **9**: oil, ^1H NMR δ 0.5-0.65 (2H, m), 0.86 (3H, d, J = 7 Hz), 0.99 (3H, s), 1.13 (3H, s), 3.6-3.9 (4H, m), and 4.8-5.9 (3H, m); **10**: oil, IR (neat) *ca.* 3400 cm^{-1}; ^1H NMR δ 0.4-0.7 (2H, m), *ca.* 0.85 (3H, diffused d), 0.95 (3H, s), 1.12 (3H, s), 3.3-4.0 (6H, m), and 4.68 (1H, s); $C_{16}H_{28}O_3$ [*m/z* 268.2038($M^{+\cdot}$)];[13] **11**: oil, IR (neat) 2725 and 1730 cm^{-1}; ^1H NMR δ 0.35-0.75 (2H, m), *ca.* 0.85 (3H, diffused d), 0.97 (3H, s), 1.14 (3H, s), 3.65-3.95 (4H, m), 4.67 (1H, s), and 9.70 (1H, t, J = 1.5 Hz); **12**:[10] oil, ^1H NMR δ 0.4-0.8 (2H, m), 0.87 (3H, d, J = 6 Hz), 0.99 (3H, s), 1.14 (3H, s), 3.42 (*ca.* 3H, s), *ca.* 3.8 (4H, m), *ca.* 5.7 (1H, m), and 6.15-6.5 (1H, m); $C_{18}H_{30}O_3$ [*m/z* 294.2213($M^{+\cdot}$)];[13] (±)-**13**: oil, IR (neat) 3350, *ca.* 1650, and 855 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.5-0.7 (2H, m), 0.72 (3H, d, J = 5.5 Hz), 0.94 (3H, s), 1.13 (3H, s), 4.17 (2H, br. s), and 5.57 (1H, br. s); ^{13}C NMR ($CDCl_3$) δ 17.0, 17.9, 18.8, 20.4, 20.5, 30.0, 30.6, 31.4, 34.2, 37.5, 43.5, 51.3, 62.5, 129.0, and 142.9; $C_{15}H_{24}O$ [*m/z* 220.1827($M^{+\cdot}$)].[13]

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References

1) A. Matsuo, S. Uto, H. Nozaki, M. Nakayama, and S. Hayashi, *J. Chem. Soc., Chem. Commun.*, 1980, 1220; numbering according to biogenetic considerations is applied for **1**. *Cf.* A. Matsuo, S. Uto, H. Nozaki, M. Nakayama, and S. Hayashi, the 24th Symposium on the Chemistry of Perfumes, Terpenes, and Essential Oils, Koriyama, September, 1980 (Proceedings, p. 227).

2) Compounds **3**-**12** are racemic. The stereostructures shown in **3**, **4**, and **5** are those for enantiomers of natural (+)-car-2-ene and its derivatives, respectively.

3) S. P. Acharya and H. C. Brown, *J. Am. Chem. Soc.*, 89, 1925 (1967). When **4** was oxidized with CrO_3-pyridine complex in CH_2Cl_2 in place of the ether-chromic acid procedure, the ketone (**5**) was obtained in a quantitative yield.

4) Y. R. Naves and G. Papazian, *Helv. Chim. Acta*, 25, 984 (1942); Y. R. Naves, *ibid.*, 25, 732 (1942). *Cf.* E. D. Andrews and W. E. Harvey, *J. Chem. Soc.*, 1964, 4636; B. Ramamoorthy and G. S. K. Rao, *Tetrahedron Lett.*, 1967, 5145. Piperitenone (**2**) was transformed into **3** in 94% yield.

5) W. Cocker, P. V. R. Shannon, and P. A. Staniland, *J. Chem. Soc. (C)*, 1967, 485. *Cf.* reference 3. The alcohol (**4**) was obtained from **3** in 90% yield.

6) C. Earnshaw, C. J. Wallis, and S. Warren, *J. Chem. Soc., Perkin Trans. 1*, 1979, 3099 and references cited therein.

7) Unchanged **5** containing a trace amount of isomerized product (caran-2-one) was also obtained in *ca.* 50% yield. The ketone (**5**) did not react with the following reagents. a) (Methoxymethyl)triphenylphosphonium chloride and butyllithium. b) Diethyl pyrrolidinomethylphosphonate and butyllithium with or without use of hexamethylphosphoric triamide [S. F. Martin and R. Gompper, *J. Org. Chem.*, 39, 2814 (1974)].

8) The aldehyde (**7**) was obtained as a sole product. The formyl group would be in a thermodynamically stable β disposition; this stereochemistry remained unconfirmed because of the signal due to C-2 position being overlapped with other signals on ^1H NMR.

9) P. Groenewegen, H. Kallenberg, and A. van der Gen, *Tetrahedron Lett.*, 1978, 491.

10) The ^1H NMR spectrum shows that this methoxymethylene derivative (**12**) consists mostly of one of the two geometrical isomers.

11) Synthetic studies of sesquiterpenic spirocycles, especially spirovetivanes, have been carried out by many groups; *e.g.*) A. Murai, S. Sato, and T. Masamune, *J. Chem. Soc., Chem. Commun.*, 1981, 904; T. Ibuka, K. Hayashi, H. Minakata, Y. Ito, and Y. Inubushi, *Can. J. Chem.*, 57, 1579 (1979), and references cited therein. Our synthesis would be remarkable in that spiro[4.5]decane system was constructed efficiently by demasking and simultaneous aldol-type condensation of a protected dialdehyde compound.

12) Measured in CCl_4 unless otherwise noted.

13) Determined by high resolution mass spectroscopy.

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