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## SYNTHESIS OF (±)-VITRENAL

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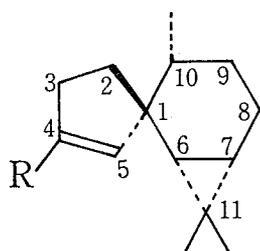
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(±)-Vitrenal (**1**), a sesquiterpene aldehyde with a novel vitrane skeleton, was synthesized from a monoterpene piperitenone (**2**) by 12-step reactions in *ca.* 7% overall yield. 2-Formyl-isocarane, derived from **2** *via* (±)-isocaran-2-one was 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.

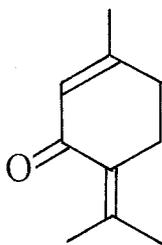
(+)-Vitrenal is a plant-growth inhibitory sesquiterpene isolated from the liverwort *Lepidozia vitrea* STEPH., its structure (**1**) including absolute configuration being determined unambiguously by X-ray diffraction analysis.<sup>1)</sup> This communication deals with a synthesis of (±)-vitrenal with a novel vitrane<sup>1)</sup> 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**),<sup>2,3)</sup> *via* car-2-ene (**3**),<sup>2,4)</sup> and *cis*-caran-*trans*-2-ol (**4**),<sup>2,5)</sup> by the known procedures. Treatment of diphenyl(methoxymethyl)phosphine oxide with LDA in THF gave its lithium derivative,<sup>6)</sup> 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.<sup>7)</sup> Acid hydrolysis (aq. HCl in THF, reflux) of the mixture (**6**) gave an aldehyde (**7**)<sup>8)</sup> in 97% yield. A stereoselective introduction of a

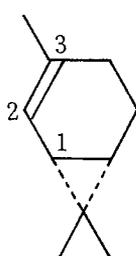


**1** R = CHO

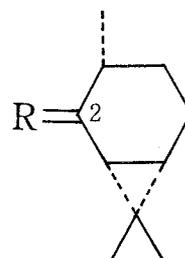
**13** R = CH<sub>2</sub>OH



**2**



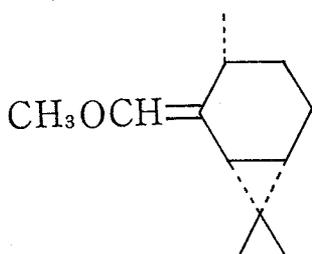
**3**



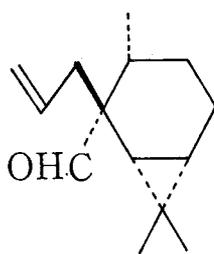
**4** R =  $\alpha$ -H,  $\beta$ -OH

**5** R = O

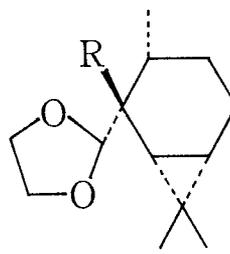
**7** R = CHO, H



**6**



**8**



**9** R = CH<sub>2</sub>CH=CH<sub>2</sub>

**10** R = CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>OH

**11** R = CH<sub>2</sub>CH<sub>2</sub>CHO

**12** R = CH<sub>2</sub>CH<sub>2</sub>CH=CHOCH<sub>3</sub>

2-propenyl group was carried out by treatment of the aldehyde (**7**) with KH in THF<sup>9)</sup> 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  $\beta$  disposition as a result of an attack of the reagent to the C-2 position from the less hindered  $\beta$ -side of intermediate enolate anion derived from **7**. This stereochemical assignment was confirmed by the transformation of **8** into ( $\pm$ )-**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<sub>3</sub>-pyridine complex in CH<sub>2</sub>Cl<sub>2</sub>. Finally, treatment of **11** with the lithium derivative of diphenyl(methoxymethyl)phosphine oxide<sup>6)</sup> in THF gave a methoxymethylene derivative (**12**)<sup>10)</sup> in *ca.* 60% yield, which was hydrolyzed (aq. HCl in THF, reflux) to afford ( $\pm$ )-vitrenal in 71% yield.<sup>11)</sup>

The <sup>1</sup>H NMR, UV, and mass spectra of the synthetic ( $\pm$ )-vitrenal were found to

be identical with those of natural (+)-vitrenal (**1**).<sup>1)</sup> Reduction of (±)-vitrenal with  $\text{LiAlH}_4$  gave the corresponding alcohol whose  $^1\text{H}$  and  $^{13}\text{C}$  NMR and mass spectral data are identical with those of the alcohol (**13**).<sup>1)</sup> 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  $\text{cm}^{-1}$ ; UV (EtOH)  $\lambda_{\text{max}}$  242 nm ( $\epsilon$  10,400);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )<sup>12)</sup>  $\delta$  0.7-0.8 (2H, m), 0.78 (3H, d,  $J = \text{ca. } 5$  Hz), 0.96 (3H, s), 1.19 (3H, s), 6.85 (1H, t,  $J = 1.5$  Hz), and 9.77 (1H, s);  $\text{C}_{15}\text{H}_{22}\text{O}$  [ $m/z$  218.1667( $\text{M}^+$ )];<sup>13)</sup> **6**: each component of the geometrical isomers (**6a** and **6b**) was separated by column chromatography ( $\text{SiO}_2$ ); **6a**(less polar on TLC): oil,  $^1\text{H}$  NMR  $\delta$  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,  $^1\text{H}$  NMR  $\delta$  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  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  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  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  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,  $^1\text{H}$  NMR  $\delta$  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  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  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);  $\text{C}_{16}\text{H}_{28}\text{O}_3$  [ $m/z$  268.2038( $\text{M}^+$ )];<sup>13)</sup> **11**: oil, IR (neat) 2725 and 1730  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  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**:<sup>10)</sup> oil,  $^1\text{H}$  NMR  $\delta$  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);  $\text{C}_{18}\text{H}_{30}\text{O}_3$  [ $m/z$  294.2213( $\text{M}^+$ )];<sup>13)</sup> (±)-**13**: oil, IR (neat) 3350, ca. 1650, and 855  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  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);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  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;  $\text{C}_{15}\text{H}_{24}\text{O}$  [ $m/z$  220.1827( $\text{M}^+$ )].<sup>13)</sup>

The authors wish to thank Soda Aromatic Co., Ltd. for a generous gift of piperitenone (**2**).

## 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<sub>3</sub>-pyridine complex in CH<sub>2</sub>Cl<sub>2</sub> 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  $\beta$  disposition; this stereochemistry remained unconfirmed because of the signal due to C-2 position being overlapped with other signals on <sup>1</sup>H NMR.
- 9) P. Groenewegen, H. Kallenberg, and A. van der Gen, *Tetrahedron Lett.*, 1978, 491.
- 10) The <sup>1</sup>H 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<sub>4</sub> unless otherwise noted.
- 13) Determined by high resolution mass spectroscopy.

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