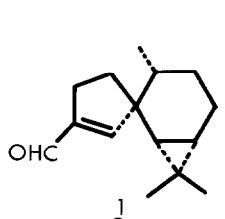
Tetrahedron Letters,Vol.27,No.10,pp 1197-1200,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

TOTAL SYNTHESIS OF (-)-VITRENAL AND ITS BIOLOGICAL ACTIVITY

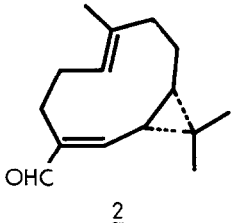
Mitsuaki Kodama*, Usman S.F. Tambunan and Tetsuto Tsunoda
Department of Chemistry, Tohoku University, Sendai 980, and
*Faculty of Pharmaceutical Sciences, Tokushima Bunri University,
Tokushima 770, Japan

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

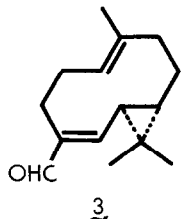
(+)-Vitrenal ((+)-1) is a tricyclic sesquiterpene aldehyde isolated by Matsuo et al. from a liverwort, Lepidozia vitrea, together with its possible biogenetic precursors, isobicyclogermacrenal (2) and lepidozenal (3) and has been shown to possess the unique structure of vitrane carbon skeleton[1]. Furthermore, all of these compounds have been shown to possess potent plant growth inhibitory activity. Because of the unique carbon skeleton and biological activity, we have synthesized (-)-1, the enantiomer of natural product, starting from (+)-Δ^3-carene[2]. The key step in the synthesis is the stereoselective creation of spirocarbon without touching the neighboring cyclopropane ring. We have successfully employed a Claisen rearrangement for this crucial step. The synthesis provided us with a rare chance to test the plant-growth regulating activity of an unnatural enantiomer. The synthetic (-)-1 behaved as a weak promotor for rice seedling.



1

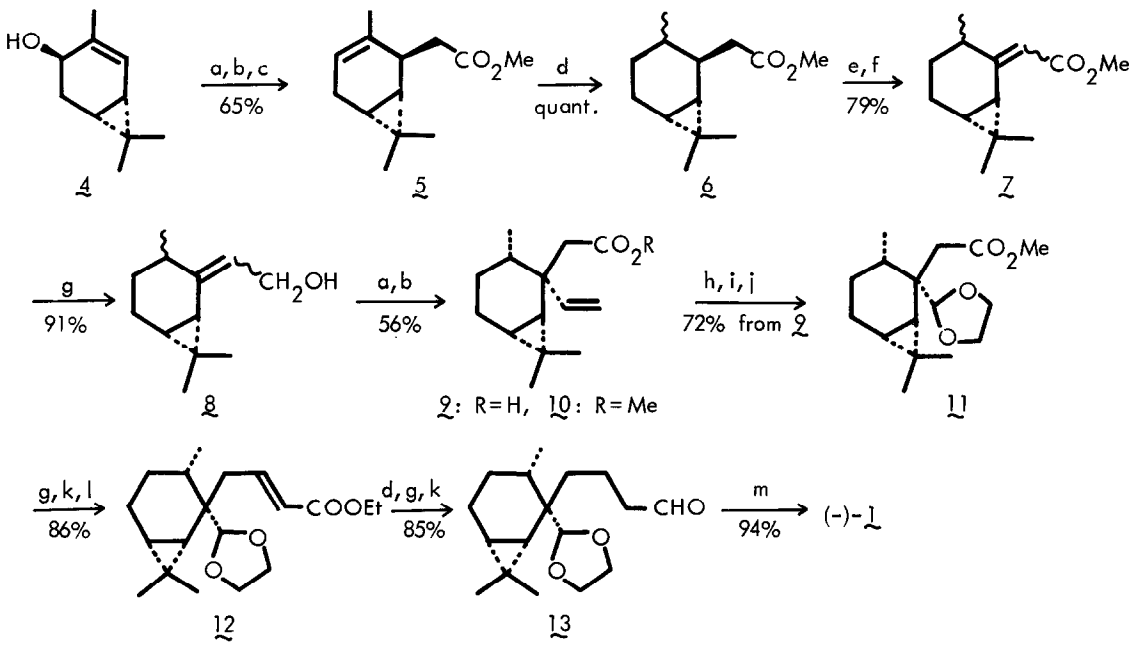


2



3

(+)-Δ^3-Carene was converted to the allylic alcohol 4 ($[\alpha]_D$ +166°) by the known procedure[3]. Heating 4 at 137° with ethyl orthoacetate in the presence of propionic acid induced Claisen rearrangement of the resulted ethoxyvinyl



a: $CH_3C(OEt)_3$, C_2H_5COOH, 137°C; b: KOH/aq. MeOH; c: CH_2N_2; d: H_2/Pd-C/MeOH, 3 atm. e: PhSeCl/LDA, -78°C; f: $NaIO_4$; g: DIBAL; h: O_3; i: Me_2S; j: HO~OH, p-TsOH; k: PCC l: $Ph_3P{=}CHCO_2Et$; m: aq. HCl/THF, reflux.

ether to furnish the ester 5 in 65% yield after alkaline hydrolysis of the product and subsequent methylation[4]. The ester 5 was hydrogenated over Pd-C to give quantitatively the saturated ester 6, gas chromatographic analysis of which revealed the contamination by its C-3 stereoisomer (ca. 5%). The configuration of sec. methyl group in 6 was assigned based on the consideration of steric requirement in the hydrogenation; the dimethylcyclopropane ring would hinder the hydrogenation from α-side[5]. Since the separation of the stereoisomers was possible only by gas chromatography, the mixture 6 was used in the further steps. Phenylselenenylation followed by oxidative deselenenylation gave the unsaturated ester 7 in 79% yield as a mixture of geometrical isomers (ca. 1:1 by GC), which was reduced with DIBAL to the allylic alcohol 8 in 91% yield. For the introduction of the second alkyl group at C-2 of 8, Claisen rearrangement was applied to the mixture 8, because the C-C bond would form from the less hindered β-side and both geometrical isomers in 8 would result in a single product. Heating 8 with ethyl orthoacetate under the conditions similar to those in the conversion 4⟶5, followed by alkaline hydrolysis yielded the crystalline acid 9, m.p. 85-7°C, in 56% yield[4]. Methyl ester (10) of the acid was shown (GC and PMR) to be a single compound[6]. Thus, all the impurities including the C-3 stereoisomer were removed completely.

For the construction of the cyclopentene ring, the double bond of 10 was

first cleaved by ozonolysis and resulting aldehyde was converted to the diethylene acetal 11, (72% from 9)[7]. Reduction with DIBAL and subsequent PCC oxidation to the aldehyde followed by Wittig reaction yielded the unsaturated ester 12 (86% yield from 11). Hydrogenation of the double bond and reduction of ester group with DIBAL followed by PCC oxidation afforded the aldehyde 13 in 85% yield. Finally 13 was heated with hydrochloric acid to induce deacetalization and aldol condensation in one pot to give the unsaturated aldehyde (-)-1 in 94% yield. The product exhibited IR and PMR spectra completely identical and the specific rotation ($[\alpha]_D$ -113°) almost completely opposite with natural (+)-1 ($[\alpha]_D$ +107°)[1].

Having the synthesis of (-)-1 completed, we have tested its biological activity as plant-growth regulator. Although the biological activities of enantiomeric pairs have extensively been investigated in the field of insect pheromones[8], the studies on growth regulators for the higher plants have, to the best of our knowledge, not carried out probably because those regulators have relatively complicated structures and the synthesis of the unnatural enantiomer is not easy. The biological test of (-)-1 using rice seedling and lettuce hypocotyl revealed a weak promotion ($P_{50}=2.18\times10^3$ ppm) in the former species and a weak inhibition ($I_{50}=27.8\times10^3$ ppm) in the latter, while natural (+)-1 showed a strong inhibition (I_{50}=18 ppm[1]) in the former species.

Acknowledgement. The authors are grateful to Dr. N. Okagami, Tohoku University, for the biological tests and to Dr. A. Matsuo, Hiroshima University, for the spectral data of natural vitrenal. Thanks are also due to Professor Shô Itô, Tohoku University, for his encouragement throughout this work.

References and Notes

1) A. Matsuo, S. Uto, H. Nozaki, M. Nakayama and S. Hayashi, J. Chem. Commun, 1220 (1980); A. Matsuo, S. Uto, H. Nozaki and M. Nakayama, J. Chem. Soc., Perkin I, 215 (1984).

2) Synthesis of (±)-1, has been published by Takahashi, et al.: H. Magari, H. Hirota, T. Takahashi, A. Matsuo, S. Uto, H. Nozaki, M. Nakayama and S. Hayashi, Chemistry Letters, 1143 (1982).

3) Z. Rykowski and K. Burak, Roczniki. Chemii., 50, 1709 (1976); K. Gollnick, S. Schroeter, G. Ohloff, G. Schade and G.O. Schenck, Liebigs Ann. Chem., 687, 14 (1965).

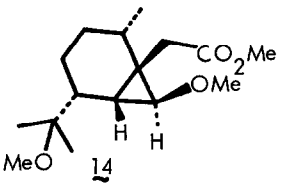
4) All the new compounds in this paper gave satisfactory elemental analyses. IR (ν) spectra were taken either neat or in KBr. PMR (δ) spectra were measured in $CDCl_3$ unless otherwise stated. $[\alpha]_D$s refer to methanol solution. Physical data of selected intermediates: 5: colorless oil, 1734 cm^{-1}; δ (CCl_4) 0.88 (3H, s), 1.03 (3H, s), 1.63 (3H, s), 3.63 (3H, s), 5.21 (1H, m); $[\alpha]_D$ +6.5° (c 1.75). 9: colorless needles, m.p. 85-87°C, ν 1693, 1634 cm^{-1}; δ 0.83 (3H, d, J=6.5), 0.99 (3H, s), 1.08 (3H, s), 2.62 (2H, s), 4.9-5.2 (2H, m), 5.96 (1H, dd, J=17.5, 10.5); $[\alpha]_D$ -145° (c 1.12). 11: colorless oil, ν 1726 cm^{-1}; δ 0.93 (3H, d, J=7.5), 1.00 (3H, s), 1.15 (3H, s), 2.49 (1H, d, J=13.5), 2.70 (1H, d, J=13.5), 3.63 (3H, s), 3.7-4.0 (4H, m), 4.78 (1H, m);

$[\alpha]_D$ -135°(c 1.12). 12: colorless oil, ν 1713, 1642 cm^{-1}; δ (CCl_4) 0.88 (3H, d, J=6.6), 1.01 (3H, s), 1.14 (3H, s), 1.28 (3H, t, J=6.6), 3.8-4.0 (4H, m), 4.11 (2H, q, J=6.6), 4.73 (1H, s), 5.73 (1H, d, J=15.6), 6.91 (1H, dd, J= 15.6, 6.6); $[\alpha]_D$ -83°(c 1.12). 13: colorless oil, ν 1715 cm^{-1}; δ 0.89 (3H, d, J=7.2), 0.99 (3H, s), 1.15 (3H, s), 3.7-4.0 (4H, m), 4.74 (1H, s), 9.77 (1H, t, J=2.3); $[\alpha]_D$ -102.5°(c 0.5). 14: colorless oil, ν 1726 cm^{-1}; δ 0.91 (3H, d, J=7.0), 1.18 (3H, s), 1.22 (3H, s), 2.25 (1H, d, J=16.3), 2.62 (1H, d, J=16.3), 3.04 (1H, d, J=3.2), 3.19 (3H, s), 3.31 (3H, s), 3.68 (3H, s).

5) This assignment was proved to be correct by the successful synthesis of (-)-1.

6) Gas chromatogram of the acidic mother liquor shows after methylation only two peaks, i.e. those of 10 (major) and its C-3 isomer (minor).

7) When the aldehyde was treated with methyl orthoacetate in the presence of p-toluenesulfonic acid at room temperature, a rearrangement of the cyclopropane ring occurred to give 14[4].



14

8) Inter al. R.G. Riley, R.M. Silverstein and J.C. Moser, Science, 183, 760 (1974). K. Mori, S. Tamada and P.A. Hedin, Naturwissenschaften, 65, 653 (1978). J.P. Vité, G. Ohloff and R.F. Billings, Nature, 272, 817 (1978).

(Received in Japan 11 January 1986)