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STEREOSELECTIVE SYNTHESIS OF (±)-PALITANTIN

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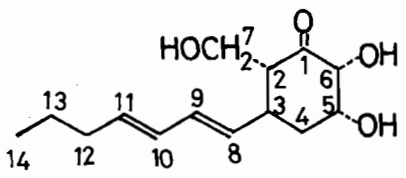
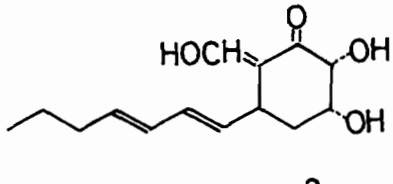
Palitantin (1) is one of the highly oxygenated cyclohexane derivatives[1], isolated from Pen. frequentans Westling together with an antibiotic compound frequentin (2).[2] The latter has been chemically derived from 1.[3] We wish to report here stereoselective synthesis of (±)-palitantin (1) and then (±)-frequentin (2) in formal sense, utilizing efficiently neighboring group effect as a synthetic strategy for regioselective reaction.[4]



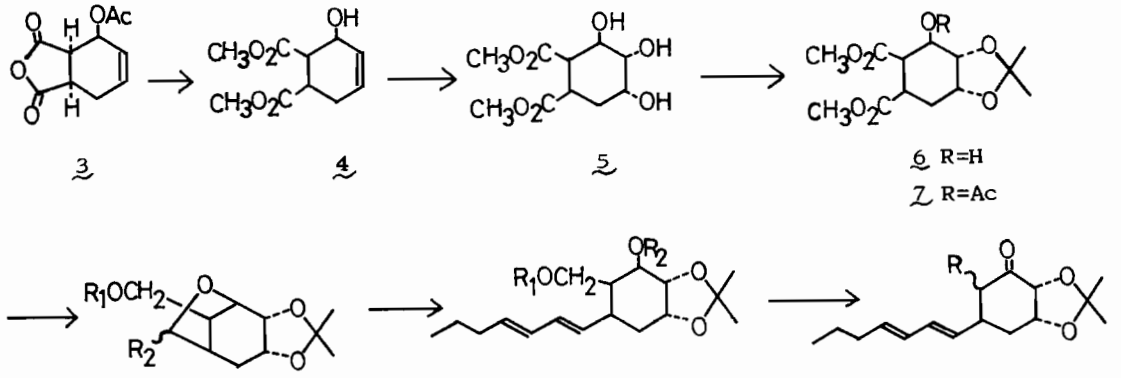
1



2

Diels-Alder reaction (toluene, reflux, 1.5 hr) of maleic anhydride and acetoxybutadiene prepared from crotonaldehyde and isopropenyl acetate[5] produced the adduct 3, mp 56~59.[6], ν_{max}^{KBr} 1850, 1780, 1735 cm^{-1}, which was treated with 3% methanolic hydrogen chloride at room temperature to yield quantitatively dimethyl ester 4, m/e 214 (M^+), ν_{max}^{film} 3400, 1730 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 3.72, 3.74 (each 3H, s, OCH_3), 4.40 (1H, bs, -CH-O). cis-Hydroxylation of the ester 4 with osmium tetroxide (THF-H_2O, $BaClO_4$, 43 hr) followed by bisulfite work up

gave a 92% of single triol 5, mp 136~137, which was readily converted to the acetonide 6, m/e 288 (M^+), $\delta^{CDCl_3}_{TMS}$ 1.35, 1.49 (each 3H, s, CH_3), 3.75 (6H, s, CO_2CH_3), 4.25 (1H, t, J=5Hz, -CH-OH). The stereochemistry of 5 was confirmed by the fact that the acetate 7 of the acetonide 6 exhibited a signal at δ 5.00 (1H, dd, J=8Hz, 5Hz, -CHOAc), whose data are compatible to stable chair conformation arising from the configuration 7.



3 4 5 6 R=H, 7 R=Ac

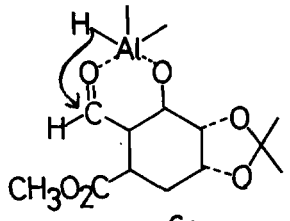
8 R_1=H, R_2=~OH
9 R_1=Ac, R_2=~OAc
10 R_1=Ac, R_2=---OH

11 R_1,R_2=Ac
12 R_1=Ac, R_2=H
13 R_1,R_2=H
14 R_1=$C(C_6H_5)_3$, R_2=H

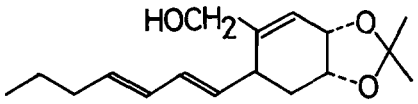
15 R=$-OC(C_6H_5)_3$
16 R=---$OC(C_6H_5)_3$

Regioselective reduction of the ester 6 was accomplished by efficient utilization of neighboring hydroxy group effect using diisobutylaluminum hydride (ca. 7 equivalents, toluene, -60°C, 3 hr) as a reducing agent to give a mixture of hemiacetals 8 mp 112~114, m/e 230 (M^+), $\delta^{CDCl_3}_{TMS}$ 5.54 (½H, s, -CH-OH), 5.67 (½H, d, J=5.5Hz, -CHOH) in 45% yield. Selective formation of the hemiacetals 8 can be rationalized assuming chelated aldehyde 6a, which by subsequent reduction was converted to 8. Direct Wittig reaction of 8 with (E)-2-hexenyltriphosphonium bromide under various conditions involved dehydration to afford nomo-ol 17. The facile dehydration would result from easy deprotonation of 2-H in Wittig reaction. Therefore, in order to prevent the dehydration the

hemiacetals were acetylated to the diacetate 9, and then hydrolyzed (acetone-



6a



17

H_2O-HCl, 12 hr) regio-and stereoselectively to the monoacetate 10, mp 115~116°, ν_{max}^{KBr} 3400, 1745 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 2.07 (3H, s, $OCOCH_3$), 5.41 (1H, s, OCH-OH), in which the acetyl group would suppress the tendency of deprotonation at 2-H by the inductive effect. Witting reaction (THF, n-BuLi, 2 hr at 5~10° and then 8.5 hr at room temperature) of the acetate 10 with (E)-2-hexenyltriphosphonium bromide gave two products 11, m/e 380 (M^+), ν_{max}^{film} 1745, 985 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 2.02, 2.12 (each 3H, s, $OCOCH_3$), 4.10 (2H, d, J=5.5Hz, CH_2OAc), 5.08 (1H, dd, J=6Hz, 4.5Hz, -CHOAc), 5.28~6.39 (4H, m, $\rightleftharpoons^{H}$), and 12, m/e 338 (M^+); ν_{max}^{film} 3460, 1740, 990 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 2.03 (3H, s, $OCOCH_3$), 3.89 (1H, dd, J=6.5Hz, 4Hz, -CHOH), 4.20 (2H, m, $-CH_2OAc$), 5.30~6.21 (4H, m, $\rightleftharpoons^{H}$) in a ratio of 4 : 1, accompanied with appreciable amount of 8. The presence of (8E, 10E)-dienyl moiety in 11 and 12 was proved by the fact that strong absorption bands at 985 and 990 cm^{-1} were observed respectively in the IR spectra. The formation of the diacetate 11 would result from intermolecular acyl migration under the reaction conditions.

Hydrolysis of 11 and 12 proceeded quantitatively to give diol 13, mp 85~87°, ν_{max}^{KBr} 3300~3600, 1620, 980 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 3.67~3.85 (2H, m, CH_2OH), 3.97 (1H, dd, J=7Hz, 4.5Hz, -CHOH). Treatment of the diol 13 with trityl chloride in pyridine afforded compound 14, which was quantitatively oxidized with chromium trioxide to ketone 15, m/e 536 (M^+), ν_{max}^{film} 1720 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 4.30 (1H, d, J=5.5Hz, CH-O). Epimerization of C-2 substituent of 15 to natural

configuration 16 was carried out by treatment of 15 with DBU for 5 hr at 25°. Removal of protective groups, trityl and acetonide groups (MeOH, TsOH, 25, 5 hr), proceeded smoothly to give (±)-palitantin (1), mp 139~141°, identical by IR, NMR, MS and chromatographic comparison with authentic material.

Acknowledgement. We are grateful to Dr. Z. Kis, Sandoz LTD, Basle, for providing us samples of natural frequentin and palitantin.

References and footnotes

1) This paper constitutes part IX of " Synthetic studies of highly oxygenated cyclohexane derivatives ". For part VIII, A. Ichihara, R. Kimura, K. Oda and S. Sakamura, Tetrahedron Lett., 4741 (1976)

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4) For general examples see B. Capon and S. P. McManus " Neighboring Group Participation ", vol. 1, Plenum, New York, N. Y., 1976. Other examples of utilization of neighboring group effects for the regioselective synthesis in this series[1] are found in a) A. Ichihara, K. Oda and S. Sakamura, Tetrahedron Lett., 5105 (1972); b) idem. Agric. Biol. Chem., 38, 163 (1974); c) A. Ichihara, M. Kobayashi, K. Oda and S. Sakamura, Tetrahedron Lett., 4231 (1974); d) K. Oda, A. Ichihara and S. Sakamura, ibid., 3187 (1975) Neighboring group effects in natural product chemistry are reviewed; A. Ichihara, Yuki Gosei Kagaku Kyokai Shi, 34, 378 (1976)

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6) Satisfactory elemental analysis and spectroscopic data have been obtained for all crystalline compounds.