SYNTHETIC APPROACHES TOWARD VERRUCARIN A. CHIRAL SYNTHESIS OF (-)-VERRUCARINOLACTONE[1]

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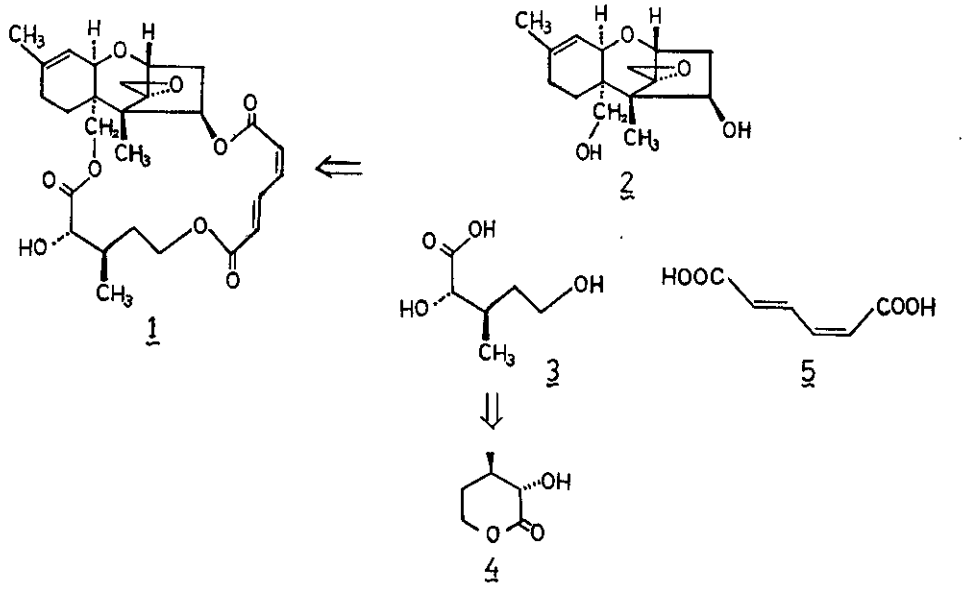
Abstract —— (-)-Verrucarinolactone ((2S,3R)-2,5-dihydroxy-3-methylvaleric acid δ-lactone) (4) was synthesized stereoselectively from an optically active butyrolactone ((S)-γ-trityloxymethyl-γ-butyrolactone) (6) as a chiral synthon.

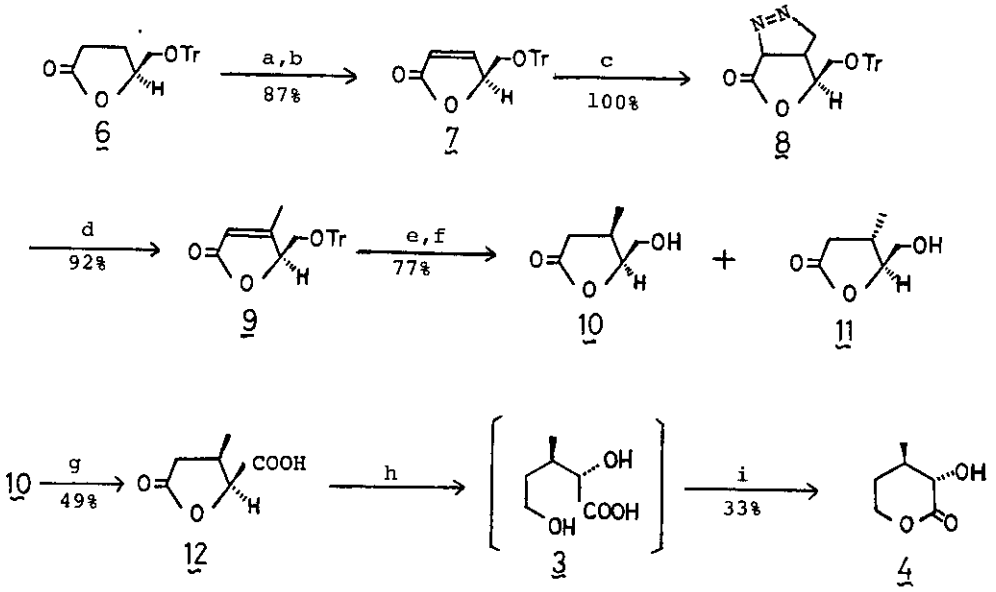
Macrocyclic trichothecane ester antibiotics such as verrucarin A (1), potent cytotoxins with significant anti-tumor activity,[2] have recently attracted much synthetic attention owing to their unique carbon skeleton as well as their pharmacological properties. Verrucarin A is composed of verrucarinic acid (3) (isolated as verrucarinolactone (4)), cis,trans-muconic acid (5) which constitute the macrocyclic portion, and verrucarol (2) as a sesquiterpene moiety.[3] While many synthetic approaches toward verrucarol[4,5] have been reported, there are a limited number of reports on the synthesis of macrocyclic portion.[6]

As a consequence of our intention to engage in the total synthesis of these compounds, we have initiated our studies to construct the macrocyclic portion in optically active form. In this communication, we wish to report a chiral synthesis of (-)-verrucarinolactone (4) from the easily available chiral butyrolactone (6).[7]

The butenolide (7),[7d] prepared from 6,[7] was treated with diazomethane[8] in THF-ether at room temperature to give the pyrazoline derivative (8) in quantitative yield. Pyrolysis of 8 in refluxing dioxane afforded the C-methyl derivative (9) in 92% yield, which has the required carbon framework of verrucarinolactone (4).

Stereoselective hydrogenation of the double bond of 9 to create a new chiral center is expected to occur from the sterically less hindered α-side to give 10,





(a) LDA, PhSeBr, THF, -78°. (b) $NaIO_4$, H_2O-EtOAc, 18-crown-6, 60°. (c) CH_2N_2, THF-ether, r.t. (d) dioxane, reflux. (e) PtO_2-H_2, EtOAc. (f) c.HCl-MeOH. (g) Jones reagent. (h) $LiBH_4$, THF, reflux. (i) HCl-MeOH.

having the requisite stereochemistry.[7a,9] Thus, 9 was hydrogenated in the presence of PtO_2 in ethyl acetate at room temperature followed by detritylation with HCl-methanol to give a mixture of two separable diastereomers (10 and 11) in a ratio of 4 to 1 in 77% yield. The structure of the major product, assigned to be 10 from the above stereochemical consideration, was supported by ^{13}C NMR analysis,[10] and was finally confirmed by converting it to (-)-verrucarinolactone (4).

The transformation of 10 to 4 only requires adjustment of the oxidation level. Oxidation of 10 with Jones reagent gave the lactone acid (12) in 49% yield. Selective reduction of the lactone function of 12 with lithium borohydride[11] in refluxing THF followed by immediate treatment of the reaction mixture with HCl-methanol gave, after silica gel column chromatography, the objective verrucarinolactone (4) (m.p. 102-102.5°, $[\alpha]_D^{22}$ -8.60°($CHCl_3$), reported[3] m.p. 103-104°, $[\alpha]_D^{22}$ -9 ± 1°($CHCl_3$)) in 33% yield. The spectral (IR and ^1H NMR) data are completely identical to those reported for the natural material.[3]

Further studies directed toward the total synthesis of macrocyclic trichothecane ester applying 6 as a chiral synthon are now in progress in our laboratory.

Experimental

All m.p.s were determined on a Büchi 510 melting point apparatus and are not corrected. IR spectra were recorded with a JASCO DS-402G or with a JASCO IRA-1 grating infrared spectrometer. NMR spectra were recorded with a JEOL JNM-PS 100 or with a Hitachi R-24 spectrometer for ^1H, with a JEOL JNM-FX 100 spectrometer for ^{13}C. Chemical shift values are expressed in ppm relative to internal TMS. Low resolution mass (MS) spectra were recorded with a JEOL JMS-01 SG-2 mass spectrometer and high resolution mass (HRMS) spectra were recorded with a JEOL JMS-DX 300 mass spectrometer. Optical rotations were measured with a JASCO DIP-181 automatic polarimeter.

(-)-3-Carboxy-4-(1-hydroxy-2-trityloxyethyl)-1-pyrazoline γ-Lactone (8) —— An ethereal solution (800 ml) of diazomethane (generated from N-nitrosomethylurea (25.0 g, 243 mmol)) was added to a solution of 7 (m.p. 152.5-154°, $[\alpha]_D^{20}$ -95.9° ($CHCl_3$), prepared from 6 in 87% yield by the reported method[7d]) (25.0 g, 56.2 mmol) in THF (70 ml), and the whole was stirred at room temperature for 2 days. Crude 8 was isolated in quantitative yield by collecting the precipitates by filtration in addition to evaporating the filtrate. Recrystallization from benzene-hexane afforded colorless prisms of m.p. 151-153°(decomp.), $[\alpha]_D^{20}$ -181.9°(c=0.99, $CHCl_3$).

IR ν_{max}^{KBr} cm^{-1}: 1760. ^1H NMR ($CDCl_3$) δ: 2.44-2.92 (1H, m, -CH-CH_2-N=), 3.02, 3.50 (2H, ABX-type double quartet, J_{gem}=10 Hz, J_{vic}=4 and 3 Hz, -CH-CH_2-OTr), 4.06 (1H, ABX-type quartet, J_{vic}=4 and 3 Hz, -CH-CH_2-OTr), 4.32-4.92 (2H, m, -CH_2-N=), 5.56-5.74 (1H, m, =N-CH-CO-), 6.80-7.50 (15H, m, $-C(C_6H_5)_3$). HRMS m/z Calcd. for $C_{25}H_{22}N_2O_3$: 398.1630. Found: 398.1663.

(S)-(-)-4-Methyl-5-trityloxymethyl-2(5H)-furanone (9) —— A solution of 8 (13.8 g) in dioxane (900 ml) was heated under reflux for 50 hr. The dioxane was evaporated in vacuo, and the residue was recrystallized from ethyl acetate-hexane to give 9 (11.8 g, 92% yield) as colorless prisms of 117.5-119°, $[\alpha]_D^{20}$ -26.5°(c= 1.04, $CHCl_3$). MS m/z: 370 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1750. ^1H NMR ($CDCl_3$) δ: 1.82 (3H, s, -CH_3), 3.16, 3.62 (2H, ABX-type double quartet, J_{gem}=10 Hz, J_{vic}=4 and 3 Hz, -CH-CH_2-OTr), 4.68-4.84 (1H, m, -CH-CH_2-OTr), 5.74-5.94 (1H, m, -C=CH-), 6.80-7.60 (15H, m, $-C(C_6H_5)_3$). Anal. Calcd. for $C_{25}H_{22}O_3$: C, 81.05; H, 5.99. Found: C, 81.05; H, 5.97

(3R,4S)-(+)-4,5-Dihydroxy-3-methylvaleric Acid γ-Lactone (10) —— A mixture of 9 (868 mg) and PtO_2 (100 mg) in ethyl acetate (25 ml) was shaken under hydrogen atmosphere (3 kg/cm^2) at room temperature for 5 hr, and was then filtered using celite. The filtrate was evaporated in vacuo, the residue was dissolved in MeOH (50 ml) containing conc. HCl-MeOH (1:99) (2 ml), and the whole was allowed to stand at room temperature overnight. The solution was neutralized by addition of K_2CO_3, filtered, and then evaporated to give a residue. ^1H NMR spectrum of this sample in $CDCl_3$ showed two doublets at δ 1.15 and 1.16 in a ratio of 4:1. A mixture of crude lactones (10 and 11) (235 mg, 77% yield) was obtained and the major isomer (10) was isolated by silica gel column chromatography with ether as a colorless oil of $[\alpha]_D^{20}$ +66.4°(c=1.01, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3440, 1775. ^1H NMR ($CDCl_3$) δ: 1.15 (3H, d, J=6 Hz, -CH_3), 2.30-2.60 (2H, m, -CH_2-CO-), 2.62-2.98 (1H, m, -CH-CH_3), 3.5 (1H, broad s, -OH), 3.84 (2H, d, J=4 Hz, -CH_2-OH), 4.44-4.66 (1H, m, -CH-CH_2OH). HRMS m/z Calcd. for $C_6H_{10}O_3$: 130.0630. Found: 130.0657.

(2S,3R)-(+)-2-Hydroxy-3-methylglutaric Acid γ-Lactone (12) —— A solution of 10 (80 mg, 0.62 mmol) in acetone (8 ml) was mixed with 2.67 M Jones reagent (0.7 ml, 1.9 mmol) and the reaction mixture was stirred under ice-cooling for 1 hr. i-PrOH (4 drops) was added and the mixture was stirred for 1 hr at 0°. Evaporation of the solvent gave a residue, which was mixed with brine, and the whole was extracted with ether. The combined extracts were dried ($MgSO_4$) and evaporated to give an oil. Silica gel column chromatography with ether afforded 12 as a color-

less oil (44 mg, 49% yield) of $[\alpha]_D^{20}$ +39.9°(c=1.29, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3460, 1785, 1745. ^1H NMR ($CDCl_3$) δ: 1.18 (3H, d, J=7 Hz, -CH$_3$), 2.17-2.86 (2H, m, -CH$_2$-CO-), 2.75-3.16 (1H, m, -CH-CH$_3$), 4.96 (1H, d, J=8 Hz, -CH-CH-COOH), 9.59 (1H, s, -COOH). HRMS m/z Calcd. for $C_6H_8O_4$: 144.0423. Found: 144.0425.

(-)-Verrucarinolactone (4) —— To a solution of 12 (92 mg, 0.64 mmol) in THF (16 ml) was added $LiBH_4$ (29 mg, 1.28 mmol) and the whole was heated under reflux for 6 hr. The solvent was evaporated in vacuo, and the residue was dissolved in MeOH (20 ml). After addition of MeOH (1 ml) saturated with HCl, the whole was allowed to stand at room temperature for 17 hr. Evaporation of the solvent gave a residue, which was purified by silica gel column chromatography with ethyl acetate-benzene (1:3) to give 4 (27 mg, 33% yield) as a colorless solid. Recrystallization from ether gave colorless prisms of m.p. 102-102.5°, $[\alpha]_D^{20}$ -8.60°(c=0.93, $CHCl_3$). MS m/z: 130 (M^+). IR $\nu_{max}^{CH_2Cl_2}$ cm^{-1}: 3540, 1735, 1220, 1110, 1090, 1060, 910. ^1H NMR ($CDCl_3$) δ: 1.26 (3H, d, J=6 Hz, -CH$_3$), 1.48-2.04 (3H, m, -CH$_2$-CH-CH$_3$), 3.40 (1H, broad s, -OH), 3.87 (1H, d, J=10 Hz, -CH-CH-O), 4.35 (2H, m, O-CH$_2$-). Anal. Calcd. for $C_6H_{10}O_3$: C, 55.37; H, 7.75. Found: C, 55.14; H, 7.96.

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