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A SYNTHESIS OF THE MARINE ANTIBIOTIC (-)-MALYNGOLIDE FROM D-GLUCOSE

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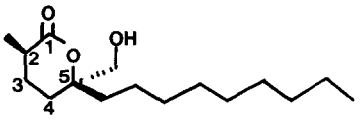
Summary (-)-Malyngolide, an antibiotic from the marine blue-green alga *Lyngbya majuscula*, was synthesized in about 30 % yield from methyl 4,6-O-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose, a chiral synthon easily derived from commercially available methyl α-D-glucopyranoside

(-)-Malyngolide 1, an antibiotic active against *Mycobacterium smegmatis and Streptococcus pyogenes*, was isolated in Moore's laboratory[1] from a shallow-water variety of the blue-green alga *Lyngbya majuscula* Gomont from Kahala Beach, Oahu The relative stereochemistry assigned[1] to C-2 and C-5 in malyngolide was confirmed by two independent syntheses of the racemic form[2,3] An asymmetric total synthesis[4] secured the absolute configuration of the natural antibiotic



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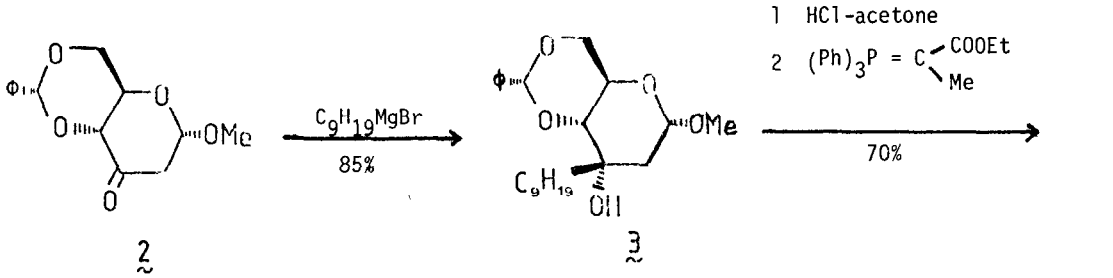
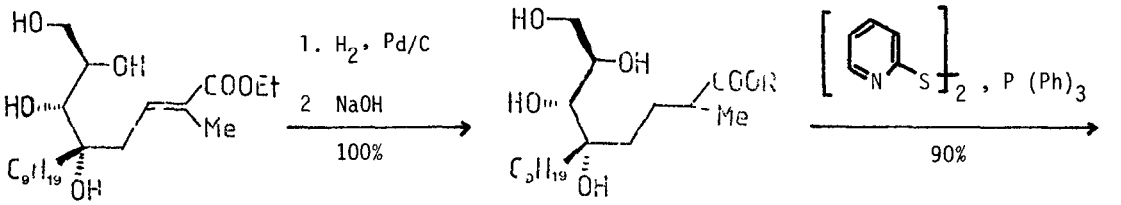
In connection with our interest in the total synthesis of optically active natural products using carbohydrates as chiral templates, we imagined a strategy in which the S configuration at C-5 of (-)-malyngolide is stereospecifically derived from C-3 of D-glucose

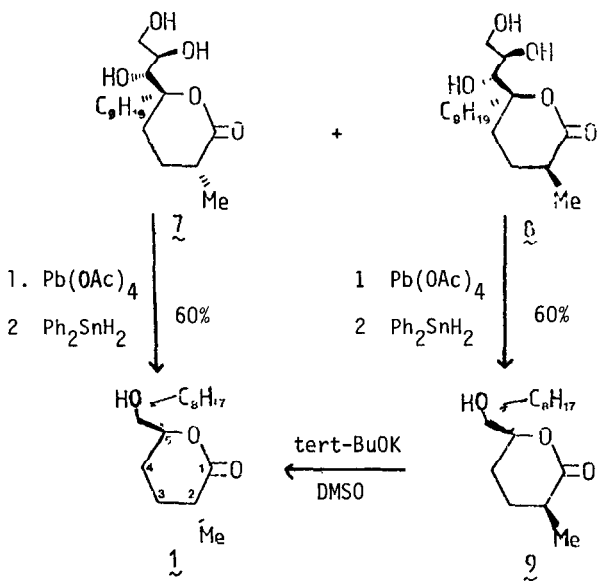
Methyl 4,6-O-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose (2) is easily prepared[5] in five steps and bulk amount from commercially available methyl α-D-glucopyranoside and was used as the starting chiral synthon Treatment of the ulose 2 with nonylmagnesium bromide in ether (0°, 3 h) stereospecifically afforded[6] the tertiary alcohol 3 (85 %), m.p 83-84°(hexane)



2 → 3



4 → 5, R = Et; 6, R = H



7 + 8 → 1 + 9

$\{\alpha\}_D$ + 60.7°[7] Acid hydrolysis (HCl 0 3 N-acetone, 2 3,v/v, 70°, 5 h) of the alcohol 3 gave a cyclic hemiacetal which was condensed without purification with carbethoxyethylidene triphenylphosphorane[8] (8 equiv.) in ethyl acetate (75 °, 20 h) to provide the E-isomer 4 as the sole product (70% from alcohol 3), m p. 65-66° (hexane), $\{\alpha\}_D$ + 13°. Compound 4 was reduced in quantitative yield (H_2, Pd/C 10 %, ethanol,0 5 h) to a diastereoisomeric mixture of esters 5 (1.1, according to ^1H n.m r), m.p. 60-61° (hexane), which were not separated at this stage The esters 5 were quantitatively hydrolyzed (NaOH 2 N in ethanol, 60°, 1 h) to the corresponding diastereoisomeric acids 6, m p 104-107° (ethyl acetate-hexane), which regiospecifically cyclized[9] (dipyridyl disulfide-PPh_3 in xylene[10], 20°, 12 h) to the epimeric δ-lactones (90 %) 7, $\{\alpha\}_D$ -14°, and 8, $\{\alpha\}_D$ + 2.7°, separated on silica gel (chloroform-acetone,7 3,v/v) Oxidative cleavage of the triol 7 (lead tetraacetate, 2.5 equiv in toluene-acetonitrile,4 1, v/v, -40°, 0 5 h) followed by reduction[11] (Ph_2SnH_2 in ethyl ether, 0°, 1 h) delivered (-)-malyngolide 1 (60 % from the triol 7), m p 36-37° (mass crystallization), $\{\alpha\}_D$ -12.7°, natural product[1], $\{\alpha\}_D$ -13°, colorless oil The n.m r. spectral properties (^1H and ^{13}C) of this hydroxy lactone 1 were virtually identical with those previously reported for the naturally occuring (-)-malyngolide .

A similar sequence of reactions was performed on the triol 8 to give (+)-epimalyngolide 9 (60 % from the triol 8), m p 29-30° (mass crystallization), $\{\alpha\}_D$ + 17°, litt [4] $\{\alpha\}_D$+ 19 1° This lactone was easily epimerized to 1 by treatment with $KOBu^t$ in DMSO, so that (-)-malyngolide was synthesized from the chiral starting ulose in about 30 % yield.

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References and Notes

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6 It is known that addition of methylmagnesium iodide to the carbonyl group of methyl 4,6-O-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose is stereospecific B Flaherty W G Overend, and N R Williams, J Chem Soc , (C), 398 (1966)

It has also been shown that addition of methylmagnesium iodide to methyl 4,6-O-benzylidene-2-deoxy-α-L-*erythro*-hexopyranosid-3-ulose is highly stereoselective giving predominantly the axially-oriented tertiary alcohol · G.B Howarth and J.K.N Jones, Can J.Chem , 45, 2253 (1967)

In compound 2 attack by the Grignard reagent from the side resulting in the formation of the expected axial alcohol 3 is sterically more favorable than attack from the side resulting in the formation of the equatorial alcohol, where a steric interaction between the attacking species and the axial methoxy group at C-1 is present

7 Satisfactory elemental analyses or mass spectra and i r and n m r. data have been obtained for all intermediates and products Optical rotations were measured for solution in chloroform at 20° C

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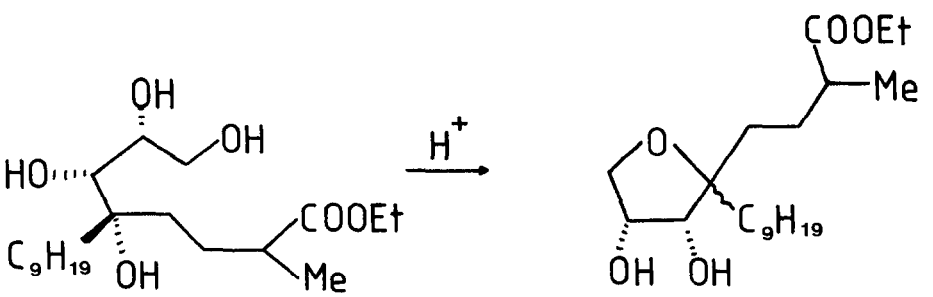
9 Attempts at lactonization under acidic conditions resulted only in dehydration to provide a substituted tetrahydrofuran, its absolute configuration at the quaternary carbon atom being not determined in this work



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