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SYNTHETIC STUDIES ON OPTICALLY ACTIVE β-LACTAMS.[1] STEREOCONTROLLED SYNTHESIS OF CHIRAL THIENAMYCIN INTERMEDIATE FROM D-GLUCOSE

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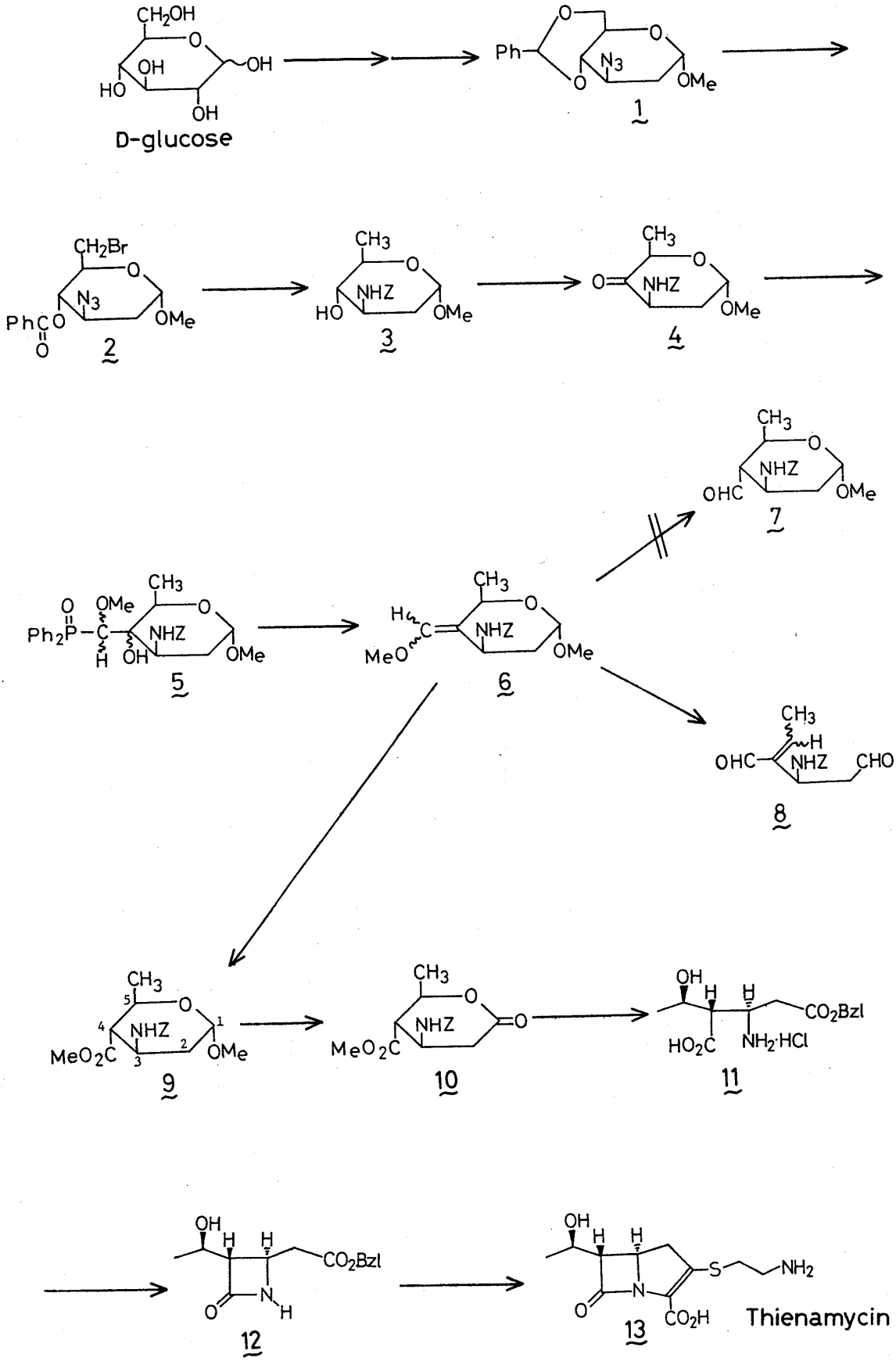
Chiral thienamycin intermediate (12) having the correct absolute configuration was synthesized from D-glucose.

KEYWORDS ——— β-lactam; thienamycin; chiral synthesis; D-glucose; pyridinium chlorochromate; Horner-Wittig reaction

Thienamycin (13), a novel β-lactam antibiotic with carbapenem structure and high antibacterial activity, has attracted a number of synthetic approaches.[3] As thienamycin possesses three contiguous chiral centers, the control of its stereochemistry is a challenging problem in the synthesis. We describe here the synthesis of optically active β-lactam derivative (12), a useful chiral intermediate for the synthesis of thienamycin,[3i] from D-glucose.[4]

Methyl 3-azido-4,6-O-benzylidene-2,3-dideoxy-α-D-arabino-hexopyranoside (1), readily available from D-glucose,[5] was transformed into the corresponding 4-O-benzoyl-6-bromo derivative (2)[6] (mp 65-65.5°C, $[\alpha]_D^{20}$ +41.9°(c=1.0, $CHCl_3$), 76%) by treatment with N-bromosuccinimide in CCl_4 containing excess barium carbonate.[7] Hydrogenation of azido group, reductive dehalogenation and debenzoylation by transesterification in one step with Raney nickel under hydrogen in the presence of triethylamine in methanol furnished the corresponding amino alcohol, which without purification was converted to the N-benzyloxycarbonyl derivative (3)[6] (mp 132-135°C, $[\alpha]_D^{20}$ +117°(c=1.4, $CHCl_3$), 52%). Oxidation of 3 with dimethyl sulfoxide-trifluoroacetic anhydride in CH_2Cl_2[8] at -65°C gave the ketone (4)[6] (mp 82-83°C, $[\alpha]_D^{20}$ +91.2°(c=1.0, $CHCl_3$), 93%). Horner-Wittig reaction of 4 with lithium derivative of methoxymethyldiphenylphosphine oxide[9] in tetrahydrofuran at -65°C gave the adduct (5)[6] as a mixture of two diastereomers (ca. 2.7:1) in 92% yield, which were separated by column chromatography (silica gel, ethyl acetate). Treatment of the major less polar isomer ($[\alpha]_D^{20}$ +60.6°(c=1.0, $CHCl_3$)) with potassium hydride (3 eq.) in dimethylformamide at 0°C gave the corresponding enol ether (6)[6] (mp 66-67°C, $[\alpha]_D^{20}$ +86.9°(c=1.0, $CHCl_3$), 75%). Some difficulty was encountered in the conversion of this enol ether (6) to the corresponding aldehyde (7) by acid hydrolysis due to the formation of undesired ene-dialdehyde (8) by β-elimination. However, this difficulty was solved by direct conversion of the enol ether (6) to the methyl ester (9). Thus, oxidation of 6 with pyridinium chlorochromate in CH_2Cl_2[10] at room temperature afforded 9[6] (mp 128°C, $[\alpha]_D^{20}$ +79.6° (c=1.1, $CHCl_3$), 30%) after column chromatography (silica gel, benzene:ethyl acetate =20:1). The stable equatorial orientation of the methoxycarbonyl group at C-4 is supported by NMR coupling constant (10 Hz) between H-4 and H-5, and no epimer at



C-4 could be detected. The stereochemistry of 9 was further confirmed by the conversion of 9 to the β-lactam (12), which is reported in racemic form.[3i] Thus, acid hydrolysis and subsequent Jones oxidation afforded the corresponding lactone (10)[6] (mp 118.5-119°C, $[\alpha]_D^{20}$ +2.2°(c=1.2, $CHCl_3$), 50%). After catalytic removal of the N-benzyloxycarbonyl group and acid hydrolysis of the methyl ester, the resulting amino acid hydrochloride was converted to the corresponding benzyl ester (11). The reaction of this ester (11) with dicyclohexylcarbodiimide afforded 12[6] as an oil ($[\alpha]_D^{20}$ +9.9°(c=2.3, $CHCl_3$), 43%) after column chromatography (silica gel, benzene:ethyl acetate=1:2). Racemic 12 is already converted to racemic thienamycin.[3i]

The synthesis of optically active β-lactam (12) described here is characterized by simplicity, efficiency, and practicality. Further studies on optically active β-lactams are now in progress in our laboratory.

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