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Preparation and Reactions of Optically Active 6-(2,4-Dimethoxybenzyl)-2-[(1',2'-O-isopropylidene)ethyl]-4-methoxy-3-oxa-7-oxo-6-azabicyclo[3.2.0]heptane.
Syntheses of 2-Amino-2,3-dideoxy(branched-chain)sugar Analogues

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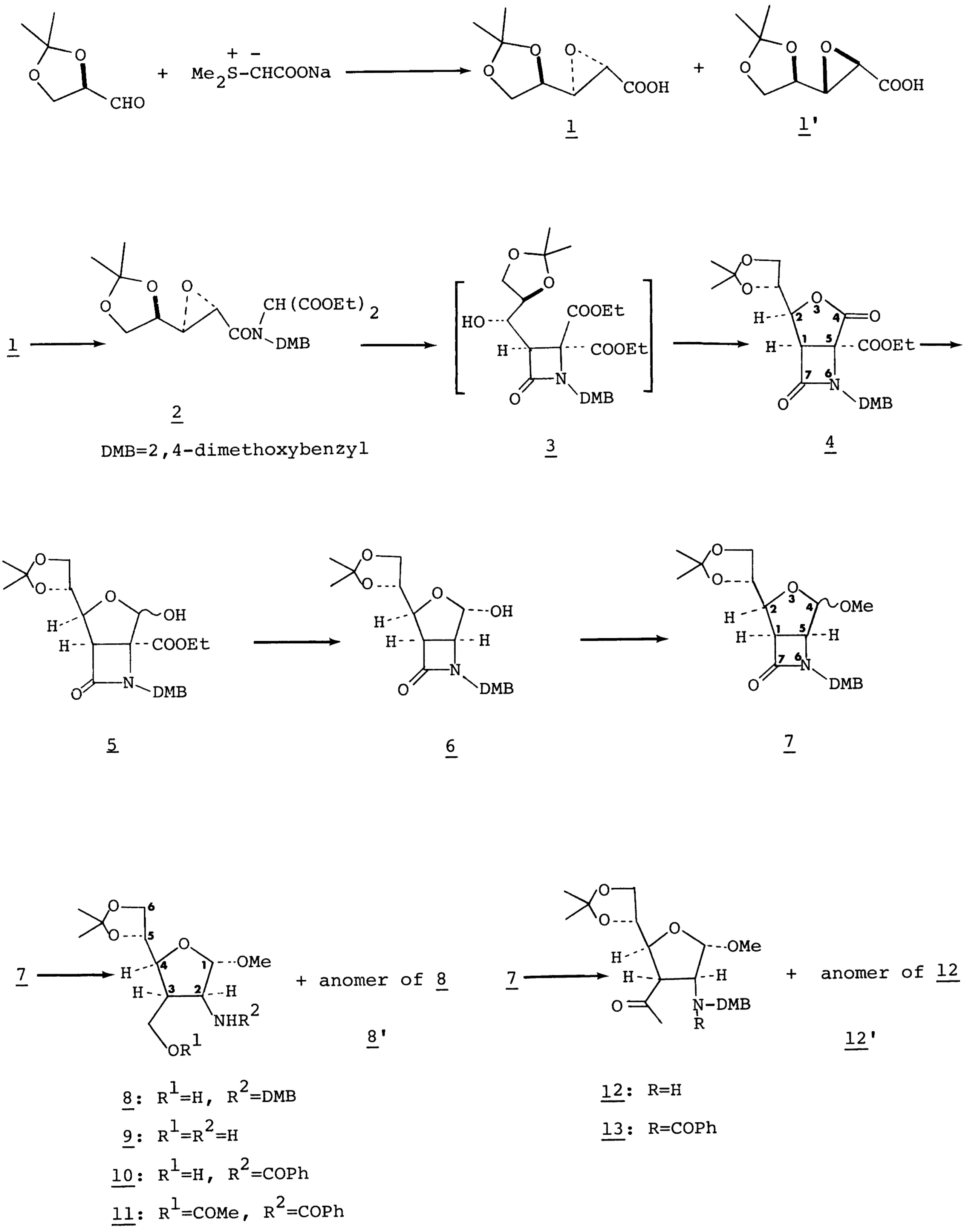
A new method for the synthesis of methyl 2,3-dideoxy-2-benzoylamido-3-acetoxymethyl-5,6-O-isopropylidene-α-D-mannofuranoside and other analogues from 2,3-O-isopropylidene-D-glyceraldehyde via a commom β-lactam intermediate is described.

The carbohydrates are an important group of naturally occurring organic compounds. Recently, their importance as components of living bodies have been increasingly recognized. Many kinds of synthetic approaches for sugars have been developed, however exploration into a new and efficient processes is still continuing. In this paper, we wish to report a preparation of optically active β-lactam intermediate (7) from 2,3-O-isopropylidene-D-glyceraldehyde, and also a new method for syntheses of 2,3-dideoxy-2-amino-3-hydroxymethyl-, -3-acetyl-, and -3-C-carboxy-α-D-mannofuranoside derivatives from 7 .

We chose an epoxycarboxylic acid (1) as a key compound which has already been synthesized by two groups.[1)] (Scheme 1). However, we attempted one step synthesis of 1 by the reaction of 2,3-O-isopropylidene-D-glyceraldehyde[2)] with dimethylthetin anion[3)] to reduce the number of steps. Thus, reaction of dimethylthetin anion, produced by treatment of dimethylthetin bromide with NaH in dimethyl sulfoxide, with 2,3-O-isopropylidene-D-glyceraldehyde at room temperature for 20 h gave a 2.6:1 mixture of epoxy acids, 1 and 1', in 77% yield. The ratio was determined by chromatographic separation of the mixture esterified by diazomethane[1)] on a silica gel column. The methyl ester of 1 was saponified with aqueous NaOH, and the optically pure acid (1) was treated with diethyl N-2,4-dimethoxybenzylaminomalonate and dicyclohexylcarbodiimide to give an amide (2) in 42% yield. Then, azeotropic treatment of 2 with catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene to remove the ethanol released during the reaction yielded bicyclic β-lactam (4) in 75% yield.[4)] When the mixture of 1 and 1' was used without separation, 4 was obtained in 22% yield

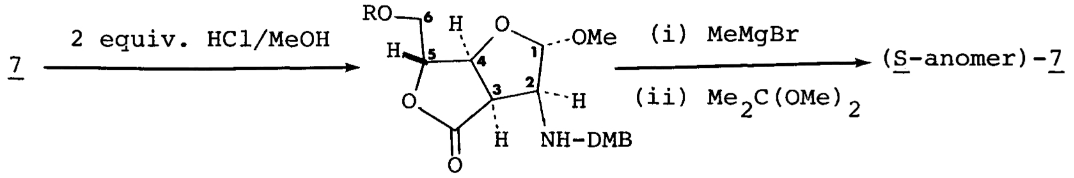


DMB=2,4-dimethoxybenzyl

8: R^1=H, R^2=DMB
9: R^1=R^2=H
10: R^1=H, R^2=COPh
11: R^1=COMe, R^2=COPh

12: R=H
13: R=COPh

Scheme 1.



14: R=H

15: R=$CMe_2(OMe)$

Scheme 2.

(two steps) after chromatographic separation. Reduction of 4 with $NaBH_4$ in EtOH containing a catalytic amount of silica gel$^{5)}$ at -40 °C gave an anomeric mixture of hemiacetal (5) in 90% yield. In this reaction, occasionally only esterification by ethanol occurs to give diester (3), quantitatively. However, this compound (3) can be converted into 4, quantitatively, by azeotropic treatment with DBU in benzene. Treatment of 5 with 0.3 equiv. of DBU in pyridine-water (20:1) at reflux temperature for 45 min gave a decarboethoxylated compound (6), mp 172-173 °C, $[\alpha]_D^{25}$ -10.5° (c 1.61, $CHCl_3$), in 79% yield, which revealed to have the S configuration at the anomeric position. Glycosidation of 6 with MeI and Ag_2O in N,N-dimethylformamide (DMF) gave a 5:1 anomeric mixture of 7 (elucidated by ^1H NMR) in 86% yield. Both of the anomers have the same R_f value on a silica gel (cyclohexane : ethyl acetate = 1:1).

Reduction of 7 with $LiAlH_4$ in tetrahydrofuran (THF) produced two aminoalcohols, 8 and 8', in 75% and 15% yields, respectively, without forming the corresponding azetidines$^{6)}$ after separation on a silica gel column. Hydrogenation of 8 in ethanol by use of 10% Pd on carbon as a catalyst gave a dedimethoxybenzylated aminoalcohol (9) in 48% yield. Treatment of 9 with 1.1 equiv. of benzoyl chloride and triethylamine in THF gave an amidoalcohol (10), which was further converted to an acetate (11) in 97% yield (two steps) as a crystalline solid, mp 120-121 °C, $[\alpha]_D^{25}$ +48.9° (c 1.1, EtOH).

Treatment of 7 with MeLi in THF after chromatographic separation gave a 3:1 mixture of a 3-acetyl compound (12) and its anomeric isomer (12') in 77% yield accompanied by some by-products. This type of reaction of the usual N,N-disubstituted amides or a single β-lactam$^{7)}$ with alkyl lithium has been well known. However, the reaction of β-lactam fused with a furanoside with alkyl lithium has not been reported, so this intramolecular reaction should provide a new method for the synthesis of 2-amino-2,3-dideoxy-3-acyl-α-D-mannofuranoside. Benzoylation of 12 with benzoyl chloride and triethylamine in THF gave compound 13$^{8)}$ in 74% yield as a crystalline solid, mp 143-146 °C, $[\alpha]_D^{25}$ +140.0° (c 1.21, $CHCl_3$).

Treatment of 7 with 2 M HCl solution (2 equiv.) in methanol at reflux temperature for 1.5 h generated a (1S)-γ-lactone (14) in 78% yield. (Scheme 2). However, surprisingly, treatment of 14 with methylmagnesium bromide in THF at room temperature, and successive treatment with 2,2-dimethoxypropane and catalytic amount of pyridinium p-toluenesulfonate (PPT) regenerated (S)-anomer of 7 in 74% yield, by an intramolecular β-lactam ring closure without occurrence of alkylation of the γ-lactone by the Grignard reagent. Treatment of the alcohol of 14 with 2,2-dimethoxypropane and PPT gave 15 as an oil.[9)]

Thus, it is clear that the β-lactam (7), obtained from 2,3-O-isopropyridene-D-glyceraldehyde in 6 steps, is a versatile intermediate for a synthesis of 2-amino-2,3-dideoxysugar analogues.

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5) Addition of a catalytic amount of silica gel (Silica gel 60, 230-400 mesh, Merck) makes the reduction rate faster.

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8) 270 MHz ^{1}H NMR of 13: ($CDCl_3$) δ; 1.305 (3H,s), 1.429 (3H, s), 2.369 (3H, s, C_3-$COCH_3$), 3.674 (3H, s), 3.806 (3H, s), 3.869-3.912 (1H, m, C_4-H), 4.06-4.18 (3H, m, C_3-H, C_6-H_2), 4.360 (1H, broad, C_5-H), 4.508 (2H, s, C_2-NCH_2Ar), 4.945 (1H, dd, J=2.9, 7.4 Hz, C_2-H), 5.051 (1H, d, J=2.9 Hz, C_1-H), 6.356 (1H, d, J=2.3 Hz), 6.510 (1H, dd, J=2.3, 8.4 Hz), 7.114 (1H, d, J=8.4 Hz), 7.230-7.310 (5H, m).
The structure of 13 was further confirmed by the X-ray crystallographic technique.

9) 400 MHz ^{1}H NMR of 15: ($CDCl_3$) δ; 1.282 (3H, s), 1.299 (3H, s), 1.920 (1H, bs, NH), 3.159 (3H, s), 3.365 (3H, s), 3.365 (1H, dd, J=6-7, 8-9 Hz, C_3-H), 3.469 (1H, dd, J=8.8, 1.0 Hz, C_2-H), 3.520 (1H, dd, J=10.7, 1.9 Hz, C_6-H), 3.734 (1H, dd, J=10.7, 2.4 Hz, C_6-H), 3.781 (3H, s), 3.826 (3H, s), 3.700, 3.867 (2H, AB-q, J=13.6 Hz, benzyl H_2), 4.680 (1H, t, J=1.9-2.4 Hz, C_5-H), 4.715 (1H, d, J=6.8 Hz, C_4-H), 4.896 (1H, bs, C_1-H), 6.428 (1H, dd, J=2.4, 8.3 Hz), 6.450 (1H, d, J=2.4 Hz), 7.126 (1H, d, J=8.3 Hz).

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