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SYNTHESIS OF METHYL HEXAACETYL-TUNICAMINYL URACIL[1)]

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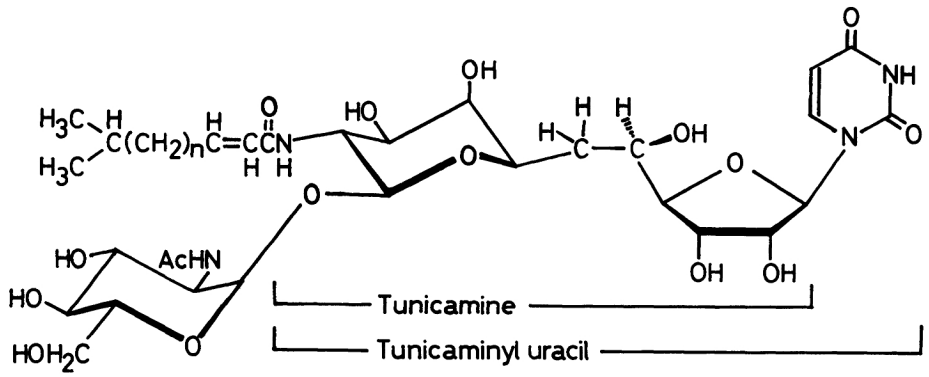
A C_{11}-carbohydrate named tunicamine, which is a component of antibiotic tunicamycins, has been synthesized in a form of polyacetyl derivative. From the tunicamine derivative, a nucleoside moiety of the antibiotic designated as tunicaminyl uracil has been successfully synthesized.

Nucleoside antibiotic tunicamycins have been isolated from a fermentation broth of *Streptomyces lysosuperficus nov. sp.*[2,3)] Since tunicamycins inhibit a biosynthesis of complex polysaccharides[4,5)] and a multiplication of enveloped viruses at any stage of the proliferation, the antibiotics show broad antiviral and antimicrobial activities.

Tunicamycin consists of heterocyclic uracil, a fatty acid, N-acetyl-D-glucosamine and a C_{11}-dialdose derivative named tunicamine.[6)] The nucleoside residue of the antibiotic which contains uracil and tunicamine has been designated tunicaminyl uracil[7)], a key intermediate for the total synthesis of tunicamycin.

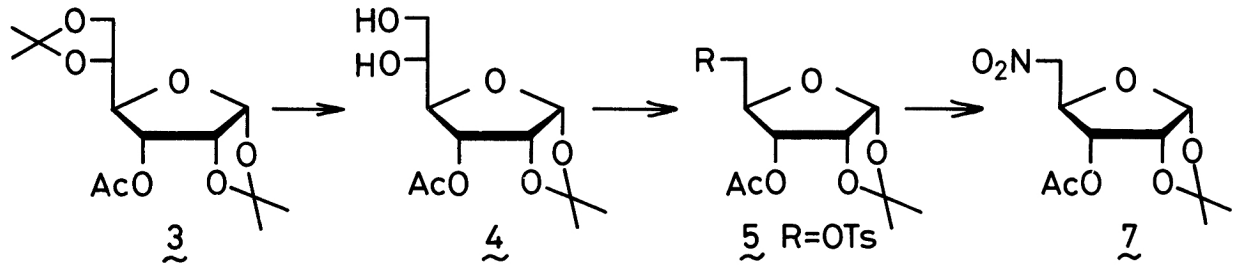
In a preceding paper[8)], a facile synthetic method of higher-carbon carbohydrates has been developed by addition of a nitro sugar to a sugar aldehyde in the presence of KF as a catalyst. By applying this method for the synthesis of tunica-



Tunicamycins (n=8,9,10,11)

mine, a precursor, methyl 9-O-acetyl-2-(benzyloxycarbonyl)amino-2,7-dideoxy-3,4:10,11-di-O-isopropylidene-7-nitro-β-L-undecodialdo-(11R)-furanose-(11,8)-pyranoside-(1,5) (8), has been obtained in a fairly good yield. In the present paper, we now wish to report the successful synthesis of the tunicamine derivative (13a) as well as the tunicaminyl uracil derivative (15a).

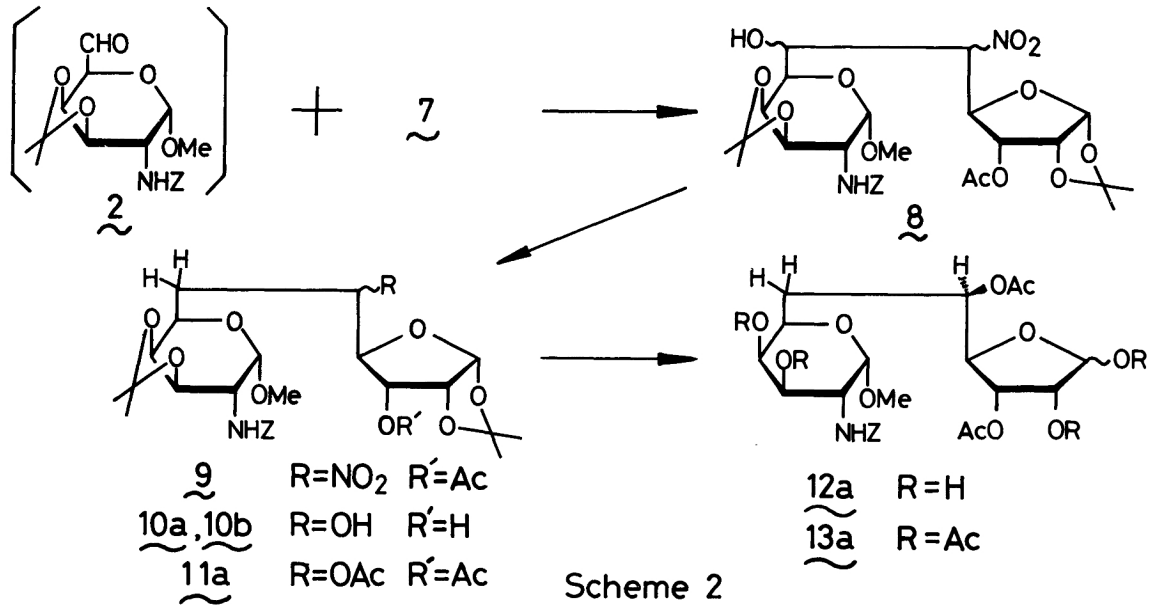
In the addition of a nitro sugar to an aldehyde, 3-O-acetyl-5-deoxy-1,2-O-isopropylidene-5-nitro-α-D-ribofuranose (7) was used as a nitro sugar, which was prepared from 3-O-acetyl-1,2:5,6-di-O-isopropylidene-α-D-allofuranose[9] (3) by a 6-step reaction in an over-all yield of 23% (Scheme 1), and methyl 2-(benzyloxycarbonyl)-amino-2-deoxy-3,4-O-isopropylidene-α-D-galactodialdopyranoside-(1,5) (2) was used as an aldehyde, which was prepared by Pfitzner-Moffatt oxidation of methyl 2-(benzyloxycarbonyl)amino-2-deoxy-3,4-O-isopropylidene-α-D-galactopyranoside (1).[10]



Scheme 1

That is, hydrolysis of 3 in aqueous acetic acid resulted in a preferential hydrolysis of the 5,6-O-isopropylidene group, giving compound (4) in 88% yield, $[\alpha]_D^{18}$ +113.7° (c 8.7, chloroform); R_f 0.38 on TLC in 1:5 (v/v) ethanol-toluene. Periodic acid oxidation of 4 and successive reduction with $NaBH_4$, followed by tosylation gave compound (5) in 62% yield, mp 95-96°C; $[\alpha]_D^{19}$ +89.0° (c 1.0, chloroform); R_f 0.54 on TLC in 1:5 (v/v) ethyl acetate-toluene. Nucleophilic substitution of 5 with NaI afforded compound (6) in 98% yield as a syrup, $[\alpha]_D^{15}$ +95.8° (c 1.1, chloroform); R_f 0.52 on TLC in the same solvent. Displacement of 6 with sodium nitrite gave 3-O-acetyl-5-deoxy-1,2-O-isopropylidene-5-nitro-α-D-ribofuranose (7) in 43% yield, mp 104-106°C; $[\alpha]_D^{19}$ +90.5° (c 1.0, chloroform).

Addition of 2 to 7 in the presence of KF in acetonitrile afforded compound (8) as a single diastereomer in 51% yield from 1, $[\alpha]_D^{22}$ +123.0° (c 1.0, chloroform); R_f 0.20 on TLC in 1:3 (v/v) ethyl acetate-toluene; ^1H NMR (90 MHz, $CDCl_3$): δ 1.34 and 1.57 (6H×2, s×2, isopropylidene), 2.08 (3H, s, OCH_3), 3.34 (3H, s, OCH_3), 5.83 (1H, d, $J_{10,11}$=3.0 Hz, H-11), 7.33 (5H, s, C_6H_5) (Scheme 2).



Scheme 2

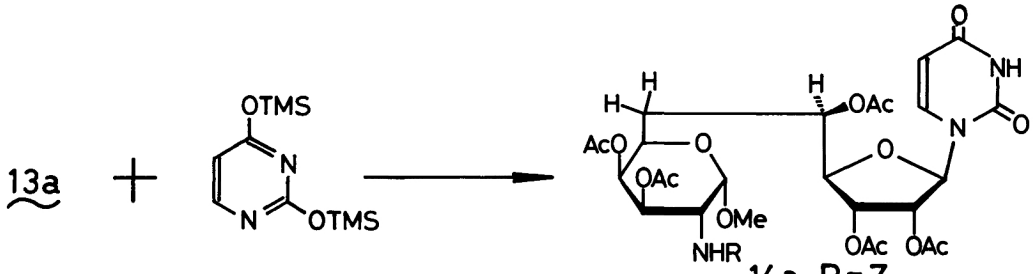
Dehydration of 8 with acetic anhydride and pyridine in chloroform, followed by hydrogenation with $NaBH_4$ gave compound (9) in 58% yield, mp 117-118°C; $[\alpha]_D^{23}$+138.6° (c 0.85, chloroform); R_f 0.40 on TLC in 1:3 (v/v) ethyl acetate-toluene.

Oxidation of 9 with $KMnO_4$ in the presence of sodium *tert*-butoxide and successive hydrogenation with $NaBH_4$, followed by hydrolysis with sodium methoxide afforded a mixture of two diastereomers (10a and 10b) in 75% yield. The mixture was separated by a silica gel column chromatography with 3:2 (v/v) ethyl acetate-toluene, giving 10a in 25.3% yield and 10b in 41.6% yield. Compound 10a, mp 154-155°C; $[\alpha]_D^{18}$ +107.3° (c 0.88, chloroform); R_f 0.19 on TLC in the same solvent. Compound 10b, syrup, $[\alpha]_D^{19}$ +93.5° (c 1.9, chloroform); R_f 0.15 on TLC in the same solvent.

Conventional acetylation of 10a gave compound (11a) in 87% yield. Hydrolysis of 11a in 60% aqueous acetic acid under reflux gave compound (12a) as an anomeric mixture. Acetylation of 12a gave compound (13a), methyl 3,4,7,9,10,11-hexa-O-acetyl-2-(benzyloxycarbonyl)amino-2,6-dideoxy-β-L-allo-D-galacto-undecodialdofuranose-(11,8)-pyranoside-(1,5), which was apparent to be a tunicamine derivative by successive reactions leading to the tunicaminyl uracil derivative.

Condensation of 13a with bis(trimethylsilyl)uracil in the presence of $SnCl_4$ in 1,2-dichloroethane afforded compound (14a) in 74.5% yield, R_f 0.43 on TLC in 1:5 (v/v) ethanol-toluene (Scheme 3).

Hydrogenolysis of 14a in methanol in the presence of Pd black in a H_2 atmosphere, followed by acetylation afforded compound (15a), 1-[methyl 10'-acetamido-2',



Scheme 3

3',5',8',9'-penta-O-acetyl-1',6',10'-trideoxy-α-L-galacto-D-allo-undecodialdo-(11'S)-pyranoside-(11',7')-furanosyl-(1',4')]-uracil, in 63% yield as an amorphous powder, mp 124-127°C; R_f 0.23 on TLC in 1:5 (v/v) ethanol-toluene; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.97, 2.00, 2.09, 2.13, and 2.20 (3H×3, 6H, and 3H, s×5, acetyl), 3.37 (3H, s, OCH_3), 5.78 (1H, dd, $J_{5,6}$=8.2 Hz, $J_{3,5}$=2.2 Hz, H-5), 5.86 (1H, d, $J_{1',2'}$= 5.4 Hz, H-1'), 7.17 (1H, d, $J_{5,6}$=8.4 Hz, H-6), 8.64 (1H, bs, H-3); Found: *m/e* 672.2282 ($M+1^+$). Calcd for $C_{28}H_{38}N_3O_{16}$: M+1, 672.2252. The ^{1}H NMR and IR spectra of 15a are superimposable on those of an authentic sample which was prepared from tunicaminyl uracil.[6]

From 10b, the corresponding compound (15b) was obtained by the analogous reaction processes, which was found to be a C-5' epimer of 15a.

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References

1) Synthetic Approach toward Antibiotic Tunicamycins. part V.
2) A. Takatsuki, K. Arima, and G. Tamura, *J. Antibiot.*, 24, 215 (1971).
3) A. Takatsuki and G. Tamura, *J. Antibiot.*, 24, 224 (1971).
4) A. Takatsuki and G. Tamura, *J. Antibiot.*, 24, 232 (1971).
5) A. Takatsuki and G. Tamura, *J. Antibiot.*, 24, 785 (1971).
6) T.Ito, Y. Kodama, K. Kawamura, K. Suzuki, A. Takatsuki, and G. Tamura, *Agric. Biol. Chem.*, 41, 2303 (1977).
7) T. Ito, A. Takatsuki, K. Kawamura, K. Sato, and G. Tamura, *Agric. Biol. Chem.*, 44, 695 (1980).
8) T. Suami, Y. Fukuda, J. Yamamoto, Y. Saito, M. Ito, and S. Ohba, *J. Carbohyd. Chem.*, 1, 9 (1982).
9) M. Haga, M. Takano, and S. Tejima, *Carbohydr. Res.*, 14, 237 (1970).
10) Y. Fukuda, H. Sasai, and T. Suami, *Bull. Chem. Soc. Jpn.*, 55, 1574 (1982).

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